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DIRECT-TO-CONSUMER ADVERTISING: MARKETING, EDUCATION, OR DECEPTION?

HEARING

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

SECOND SESSION

MAY 8, 2008

Serial No. 110–114



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U.S. GOVERNMENT PRINTING OFFICE

54–104 PDF WASHINGTON : 2008

For sale by the Superintendent of Documents, U.S. Government Printing Office
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DIRECT-TO-CONSUMER ADVERTISING: MARKETING, EDUCATION, OR DECEPTION?

THURSDAY, MAY 8, 2008

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, D.C.

The subcommittee met, pursuant to call, at 10:05 a.m., in room 2123 of the Rayburn House Office Building, Hon. Bart Stupak [chairman of the subcommittee] presiding.

Members present: Representatives Dingell (Ex Officio), Stupak, Waxman, Green, Shimkus, Whitfield, Walden, Burgess, Barton (ex officio), and Ferguson.

Staff present: John Sopko, Scott Schloegel, Paul Jung, Joanne Royce, David Nelson, Kyle Chapman, Alan Slobodin, Karen Christian, and Whitney Drew.

Mr. STUPAK. This hearing will come to order. Today we have a hearing entitled "Direct to Consumer Advertising: Marketing, Education, or Deception?" Each member will be recognized for a 5-minute opening statement. I will begin.

OPENING STATEMENT OF HON. BART STUPAK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. STUPAK. Nearly 10 years ago, the U.S. Food and Drug Administration relaxed its rules relating to direct-to-consumer advertisements for prescription pharmaceutical products. Since then, spending on DTC ads has increased from about $1.1 billion in 1997 to about $4.2 billion in 2005. This nearly 300 percent increase in DTC ad spending dwarfs the 86 percent spending increase in advertisements to physicians and the 103 percent spending increase in research and development over the same period of time.

The pharmaceutical industry insists than DTC ads are mainly an educational endeavor designed to educate consumers about new products. Research shows that some DTC advertising results in patients seeing their doctors and discussing previously undiagnosed conditions.

We must acknowledge that direct-to-consumer ads are also designed to market and sell these products. Research has shown that DTC advertising may result in advertised drugs being prescribed when a similar, less-expensive drug may have been just as appropriate. Every $1 spent on direct-to-consumer advertising results in up to a $6 increase in sales. One study demonstrated that every $1,000 spent on direct-to-consumer advertisements resulted in 24 new prescriptions.

The purpose of the hearing is to examine the potentially misleading and deception tactics used in direct-to-consumer advertisements for prescription pharmaceutical products. Our hearing today will examine three specific television advertisements: ads for Lipitor featuring Mr. Robert Jarvik, "Food and Family" ads for Vytorin, and "cancer fatigue" or "quality of life" ads for Procrit.

Pfizer's Lipitor ads featured Robert Jarvik, an individual who has never held a license to practice medicine and has never been allowed to prescribe a medication. For his participation in these ads, he was paid $1.35 million; however, none of his ads indicates that he was compensated for his appearance. In addition, Mr. Jarvik states in one of these ads that he himself takes Lipitor. Yet, he admitted in an interview that he did not begin taking Lipitor until a few months after he began filming his commercials. These ads are in violation of the American Medical Association guidelines concerning the involvement of health professionals in DTC advertisements. Mr. Jarvik's ads help maintain Lipitor's position as the most prescribed anti-cholesterol "statin" drug.

[Video shown.]

Merck and Schering-Plough's ads for Vytorin resulted in $5 billion in sales in 2007. However, while these ads appeared on the airwaves, the release of an important study examining Vytorin's ability to stop cholesterol build-up was delayed and suppressed by the companies. Significant and valuable results from this study were delayed for 2 years, while Vytorin was continuously marketed to consumers.

We now know that Vytorin has no effect on cholesterol build-up; however, this information came to us about 2 years too late. Many consumers may not have taken Vytorin had they been aware of the study results, especially since a less expensive, equally effective generic drug, Zocor, was readily available. In addition, taxpayer dollars may have been needlessly spent of Vytorin through Medicare Part D as the drug was marketed to consumers while the company sat on its study results.

[Video shown.]

Johnson & Johnson's Procrit was approved by the FDA to treat chemotherapy- and dialysis-induced anemia. Yet for 7 years, it was marketed directly to consumers for the treatment of "cancer fatigue" in order to improve the "quality of life" for patients. This was clearly an instance of off-label marketing, a practice that is prohibited by the FDA. No only did the company advertise the drug, but the FDA did very little to stop them.

[Video shown.]

These are three examples of drug companies acting improperly. Our goal today is to expose the deceptive and misleading aspects of each of these television ad campaigns, but also those of DTC ads in general. We also intend to explore better practices for direct-to-consumer marketing.

Both the Lipitor ads with Mr. Jarvik and the Vytorin "food and family" ads were voluntarily withdrawn shortly after our subcommittee began investigating direct-to-consumer ads in January of this year. However, American consumers should not have to rely on the oversight function of Congress to make sure drug companies tell the truth in their advertisements. It is likely that direct-to-con-

sumer ads will continue, and pharmaceutical companies may continue using these same questionable practices that were used in these three ad campaigns.

The FDA Division of Drug Marketing, Advertising and Communication, DDMAC, is responsible for regulating direct-to-consumer ads. Drug companies are required to submit copies of their ads at the same time that they are disseminated, but no pre-clearance is yet required. If a direct-to-consumer ad is found to be in violation of FDA regulations, FDA can issue warning letters for serious violations, which may lead to regulatory action by the FDA. However, if a company refuses to comply, the FDA cannot impose fines, except through administrative hearings. In other words, the FDA is toothless.

Today we will hear from several witnesses, including the three pharmaceutical companies responsible for the Jarvik "food and family" and "cancer fatigue" campaigns. We will also hear from Kaiser Family Foundation about the effects of direct-to-consumer ads, the American Medical Association, regarding their policy on the portrayal of health professionals in DTC ads, and the Government Accountability Office concerning FDA's rules in regulating direct-to-consumer ads. We will also hear from Dr. Ruth Day from Duke University, who will provide an overview of research on how people understand and remember information in drug ads and how to improve their ability to do so. We will learn some of the techniques used in broadcast advertisements that affect how consumers process the information in direct-to-consumer ads. This information may reveal that it is not simply a matter of what is said in a direct-to-consumer ad, but more importantly, what people take away from it.

The United States is only one of the two countries that allows direct-to-consumer ads. Pharmaceutical companies should consider it a privilege to be allowed to air direct-to-consumer ads in this country. As with all privileges, there are responsibilities, and we should make sure that pharmaceutical companies conduct themselves responsibly. The Food and Drug Administration shares the responsibility to make certain that drugs are marketed responsibly to consumers. I also believe that Congress shares the responsibility, and I intend to make certain that our committee ensures the pharmaceuticals market their products properly. I believe that Congress needs to decide whether the U.S. should continue to be one of only two countries in the world that allows direct-to-consumer ads, and if we continue to allow such advertising, whether any further limits on direct-to-consumer ads should be required. The three ads that we will discuss today are indicative of typical direct-to-consumer ad campaigns. It appears that we need to enforce significant restrictions on direct-to-consumer ads to protect American consumers from manipulative commercials designed to mislead and deceive for the profit of pharmaceutical companies.

I look forward to the testimony of each witness today, and it is my sincere hope that today's hearing will lead to a better understanding of the effects of direct-to-consumer advertisements and their proper role in our health care system.

Mr. STUPAK. I will next turn to my friend for an opening statement, Mr. Shimkus of Illinois.

OPENING STATEMENT OF HON. JOHN SHIMKUS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. SHIMKUS. Thank you, Mr. Chairman.

Today, this subcommittee will conduct oversight on direct-to-consumer advertising by drug companies. This topic has long been a controversial one. I think part of the frustration on our side is that some of the premises are not correct, because last fall, when the Subcommittee on Health and then the full committee passed the FDA Amendments Act of 2007, we created a new standard that statements in drug ads must be clear, conspicuous, and neutral. We had to weigh concerns about First Amendment and commercial speech rights of companies against concerns that drug ads were misleading and confusing.

And before we get started, I think we need to be clear about FDA's authority with respect to drug ads. Contrary to the statement in the Majority staff memo for this hearing that states, and I quote, "If a company refuses to comply with FDA or untitled or warning letters, the FDA cannot impose fines or other punishments, but must instead pursue an injunction from the courts." The FDA Amendments Act specifically gave the FDA power to impose civil fines on companies. Section 104 of the Act amends Section 303 of the Food and Drug and Cosmetic Act and provides that FDA may impose civil fines on companies when the direct-to-consumer ads are identified as being false and misleading. Granted, the FDA has only had this authority since the Act was passed last fall, and the Act just went into effect 1 month ago, but they do have the power to impose these civil fines.

And that is part of the frustration. We strengthened the law. We gave the FDA power to act, and we haven't really given them time to really impose the civil fines on false and misleading ads. This leads me to my concern about the timing of this hearing. This is a hearing of the Subcommittee on Oversight and Investigation. Our job is to uncover facts and see where the facts take us. While I believe that oversight of the drug advertising is important and necessary, I wonder if this is the appropriate time to be debating these issues, at least for some of the topics we will be discussing today.

As I mentioned earlier, the FDA Amendments Act, which was signed into law last fall, created a new standard for statements in broadcast drug ads. The regulations to interpret this standard are still being drafted. We have given FDA new power to impose fines on companies that make false and misleading statements in ads. Yet today we are reviewing three ad campaigns that were in place before the new law was enacted, and they are now off the air. Pfizer pulled its ads for Lipitor, and Merck/Schering-Plough pulled its ads for Vytorin in January. Johnson & Johnson's Procrit ads have been off the air for 3 years.

There have been a number of suggestions in the media and elsewhere about why these ads were pulled. Some have concluded that the fact that they were pulled is an admission that the ads were misleading or deceptive. Before we make any conclusion about these ads, I think we need to take a careful look at the evidence. So far the companies have produced thousands of pages of documents, perhaps even hundreds of thousands of pages about these ads. These documents show how they were drafted, the rough draft

of the ads, the companies' communications with advertising campaigns and with FDA's Division of Drug Marketing, Advertising, and Communications. We need to determine what the companies knew about the science supporting these advertising at the time they created the ads. In the case of Vytorin and Procrit, the Committee is still investigating the issue of what the companies and knew, and in particular, when they knew it. This is a long way between finding that language in an ad may be confusing or not as clear as possible and concluding that there was an intent to deceive. We need to be careful about drawing conclusions before we have had a chance to review all of the evidence before us.

I also think it is important to take a step back and put these ads into perspective. Americans see these ads all of the time, maybe even every day. Research from the Kaiser Family Foundation and a representative from the foundation that is testifying today shows that two-thirds of Americans believe that these ads helped educate them about diseases that they may not have been aware of and about available treatment. With regard to what people did after seeing the ad, the foundation's research shows that the vast majority of people, almost 70 percent, have not talked to their doctors about drug ads they have seen. Of those who did, the doctors responded in a variety of ways, including recommending lifestyle changes, recommending another prescription, recommending the drug in the ad, or recommending the over-the-counter drug. In this sense, an argument could be made that ads for drugs prompt a conversation that needs to happen between doctors and patients about patients' health and about how a patient should be treated.

In addition to balancing these benefits, we need to remember that there is a First Amendment concern at play here. The case law consistently supports the right of companies to engage in commercial speech. Of course, that speech cannot be misleading or false, and it is the FDA's job to ensure that this does not happen. We need to take a look at FDA's review of these ads, whether their system is designed to pinpoint the ads that contain false or misleading statements, and whether the Agency is taking action. Again, this is an unusual time to be looking at this issue, when Congress just changed the standard to require a clear, conspicuous, and neutral statement about the side effects, and this standard did not apply to the ads before us today.

I also look forward to the testimony of the American Medical Association and its thoughts about the role of these ads and the appropriateness of physicians serving as spokespeople. And once again, I welcome Marcia Crosse of GAO, and I am interested to see what developments have taken place since GAO issued its report in 2006 on direct-to-consumer advertising of drugs. If the purpose of this hearing is to improve the accuracy and the clarity of drug advertising, I am happy to work with Chairman Stupak and the subcommittee members on this issue in a constructive way.

Again, I thank Chairman Stupak for convening this important hearing, and I yield back my time.

Mr. STUPAK. I thank the gentleman. Mr. Green for an opening statement, please.

OPENING STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. GREEN. Thank you, Mr. Chairman. I thank you for holding the hearing today on direct-to-consumer advertising.

From 1997 to 2007, spending on DTC advertising increased by almost 300 percent, to $4.2 billion from $1.1 billion. Research has shown that for every dollar spent on DTC advertisements, companies gain $6 in increased sales. In my opinion, when discussing DTC advertising, we only have to say one word, and that is Vioxx. When it became painfully clear that the effect of direct-to-consumer advertising on the demand for the drug. Upon its approval, Vioxx was indicated for a small subset of the population who experienced pain and arthritis, but who couldn't tolerate other drugs. Vioxx was never intended for the vast number of Americans who suffer from arthritis and joint pain, and yet the drug's advertisement painted a picture of pain-free life, as if Vioxx was the next best thing since sliced bread. Soon enough, patients were asking doctors for Vioxx and sales began to skyrocket. The ads were so persuasive that it became unclear to many Americans, including some in our own families, that Vioxx wasn't readily available to the public without a prescription, and maybe a prescription was actually needed. We know from the example of Vioxx that not all products are safe, even after the approval of the FDA. And post-market studies are necessary to ensure the patients' safety.

However, many drugs are heavily marketed through DTC advertisements and consequently, a large number of patients are exposed to a significant number of health risks. In this hearing, we will look at several different issues with DTC advertisements. Pfizer's Dr. Jarvik advertisement and the misleading information it contained when patients see an advertisements with a world-renown inventor, who they think is a doctor or celebrity, they believe the product is safe, and yet we soon discover that Dr. Jarvik was not a licensed physician. We will also be discussing the Procrit advertisements which show cancer patients having increased energy after Procrit. The FDA never approved Procrit for treatment of fatigue. In fact, Procrit was approved to prevent the need for blood transfusion in a very specific group of patients. The Committee will also look at the Vytorin ads and the fact that they were still being broadcast when the study on it effectiveness was delayed for 2 years. The FDA determined the ads violated policy by not including a disclaimer on the effectiveness of Vytorin.

We should remember there is no way we can determine the full range of risk based on clinical trial alone, and in essence, once the drug is in the marketplace, it becomes the new clinical trial, and DTC does increase the number of individuals who go to their physician, but at the same time, it increases the likelihood that more people will be exposed to any number of negative effects of these drugs before they are thoroughly tested.

Mr. Chairman, again, I thank you for holding the hearing. I will yield back my time.

Mr. STUPAK. I thank the gentleman. Mr. Burgess for an opening statement, please? We have five votes on the floor, but we are going to try to get as many openings in as we can before we leave.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Dr. BURGESS. Thank you, Mr. Chairman. I appreciate your courtesy, and thank you for holding today's subcommittee hearing on the issue of direct-to-consumer advertising. It is an important aspect of one of the things that we are obligated to have under our study here at our committee.

One of the things that concerns me greatly is the issue, and we just heard Mr. Green talk about Vioxx, of aftermarket surveillance, Mr. Chairman. This committee did a great deal of work with the FDA reauthorization last summer, and the Reagan-Udall language in that legislation, which was to allow for post-market surveillance, which was to allow the exact same of surveillance to which Mr. Green just alluded, was unfortunately not funded in the USDA appropriations bill last summer, for reasons, quite frankly, I don't understand. We managed to do several earmarks in that appropriations bill, but can't seem to find the money to fund the very critical aftermarket surveillance, which would answer some of the questions that we have here in front of us today.

I will just say in my years as a practicing physician, I wasn't a great fan of direct-to-consumer advertising, but I recognize it does have a function in patient education. Certainly, the Vytorin commercial that you aired for us just a few moments ago has never been my favorite commercial. I have sometimes wondered about the actual content of that commercial, but it does provide a bit of patient education in that there are two sources for elevated cholesterol, and it is important for patients to understand that if they are going to play an active role in the maintenance of their health and the ability to lower their cholesterol function overall.

Dr. Jarvik's appearance on the other commercial that you aired, I am trying to see where the inappropriateness of that occurred. I have reviewed the criteria that was laid out for us by the president of the AMA. I will confess to you that I don't see the problem that was in that ad. There is no question that the introduction of statins into the armamentarium of the average primary care physician has made a big impact on the reduction of hearth disease in this country, and as a consequence, I think it is 800,000 premature deaths from cardiac disease have been prevented by the introduction of those types of medicines, so there has been significant savings to the Medicare program because of the introduction of these types of medications, so it is, to me, a little bit of a mystery why we are including that in the body of evidence that we are studying today.

Mr. Chairman, there are a variety of things that go into the decisionmaking process between a doctor and a patient when the decision time comes for prescribing a medication. This is something that came home to me when we were undergoing the process of rewriting the FDA Reauthorization Bill last summer, and the enormous responsibility that is laid upon each of us on this committee to do the correct thing so that the practice of medicine is not compromised in this country. I want us to be very, very careful as we proceed down this road, because honestly, I can see that we could make some decisions that would be not in the best interest in allowing the physician and the patient to have all of the information before them when they make decisions. I mean, after all, we want

there to be more transparency in the practice of medicine today. We want our patients to become more active participants in not just the maintenance of their health but the treatment of their disease, and this is yet one additional tool that is available to them.

And one other thing I would just say, and I will be interested when we hear from the GAO testifying today, the bar graphs that show the increase in the amount of direct-to-consumer advertising that has occurred since 2004, and I just am curious as to whether or not we subtracted the public-service-type announcements like for the PPA bus that Montel Williams takes around the country, if that type of advertising is included in that block of data shows an increase. I am curious about that because the amount of time and effort that was spent of marketing drugs to treat erectile dysfunction seemed to me to be disproportionate. And I have always considered that the companies would do themselves a great favor by increasing the public-service part of their announcements and not just the marketing of lifestyle drugs.

But it is an interesting topic, Mr. Chairman. It is a timely topic, and I will yield back the balance of my time.

[The prepared statement of Mr. Burgess follows:]

STATEMENT OF HON. MICHAEL C. BURGESS

Thank you Mr. Chairman and Ranking Member Shimkus.

Today the Health Subcommittee is also holding a hearing on the issue of stem cells; therefore, unfortunately, I will be splitting my time today between these two hearings. I apologize in advance for my attendance.

Mr. Chairman, as the only member of this subcommittee to have actually had a patient come to them after watching a direct-to-consumer advertisement, I'd like to offer my perspective. At times, I did have patients that came to me and asked for a certain medication because they saw the proposed benefits of a drug that was advertised and had self-diagnosed themselves. This is a reality, it does occur. However, as the physician, it was my responsibility to diagnose the patient, and it was my responsibility to write the prescription for the medicine. This responsibility isn't abdicated just because a patient watches an ad on TV.

While direct-to-consumer ads are made for the benefit of marketing specific drugs, in my opinion, the true benefit is that they make people stop and think about their health problems and then seek medical attention. Mr. Chairman, I think we can all agree that society in general benefits when people are proactive with the healthcare needs.

However, I clearly don't believe that direct to consumer advertisements should ever be misleading or deceitful. That's one of the reasons that I supported, along with the bipartisan leadership of this Committee, H.R. 3580, The FDA Amendments Act of 2007. This legislation, which was just signed into law on September 27, 2007, addressed this very issue. HR 3580 amended the Food, Drug and Cosmetic Act to 1) require that the major statement about side effects be clear, conspicuous and neutral, and 2) that the FDA has the power to impose civil fines when ads have false or misleading statements.

Mr. Chairman, this newly enacted legislation deals with this very issue we are discussing today. Couple this with the fact that the Food and Drug Administration, the Agency that has the power to enforce this law wasn't asked to testify, I'm not really sure of the purpose of this hearing.

I yield back the remainder of my time.

Mr. STUPAK. I thank the gentleman, and as a member of this committee, and a physician, I hope you will stay at least through our first panel. I think you will find it very educational from a perspective of a physician and also a member of this subcommittee.

Dr. BURGESS. If the chairman will yield, just as a housekeeping issue, we do have the other hearing going on as stem cells.

Mr. STUPAK. Right, I realize that. That is why I said that. You have been an active member. I just want to give you a double opportunity to get educated today.

Mr. Waxman?

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Mr. Chairman. Both the good doctor and I are involved in both subcommittees, so we are going to be doubly educated on two different topics today, but I appreciate the fact that you are holding this hearing, because the United States is one of only two countries in the world that permits direct-to-consumer advertising of prescription drugs. After all, these are not over-the-counter drugs. A doctor has to give a prescription. And yet the billions of dollars in advertising directed to consumers pays off, because there is an increase in the purchase of drugs.

Now, if we look at an ideal world, one would hope that the FDA would be approving a drug, and we would know that it is going to be absolutely safe and effective. That is what their objective is supposed to be, but we don't live in a perfect or ideal world, and when a drug first goes on the market, we don't have every confidence about its safety. Sometimes we have to wait for a greater population to use the drug before safety problems do occur. Now, if FDA has no other choice but to approve drugs based on this imperfect knowledge, they have to wait, then, because their preapproval is much smaller. So we look to what the Institute of Medicine has to say about this matter, because they have studied it carefully.

In 2006 they had a groundbreaking study, and they expressed some serious reservations about direct-to-consumer advertising. In their report, they cited the distortion of drug usage practices caused by DTC ads, in which the use of more expensive drugs are increased, but there may be effective drugs that are less costly, especially if they are lower-cost generics, that are not being used because of the heavy advertisement steering consumers to the more expensive drugs. The IOM also described the mixed effects that DTC has as an education tool. It conceded that consumers might learn about conditions or disease through a DTC ad that they might not otherwise have been aware about. On the other hand, the report cited that many ads overstate the benefits of a drug while understating the risks. Well, that is the commercial advantage of the drug manufacturer, and the IOM said that the DTC ads have an impact when people don't get the full information.

Physicians themselves provide evidence that DTC ads do work. Surveys vary but roughly half of the physicians report that when a patient asks them for a specific drug, they prescribe it. Well, the IOM recommended that FDA be given some new authorities aimed at DTC advertising, specifically out of a concern about that rapid uptake of new drugs with unknown risks caused by DTC ads. The IOM thought Congress should give FDA the authority to restrict advertising on a case-by-case basis during the first 2 years when a drug is on the market. When we considered FDA amendments last year, we tried to include that kind of provision. The original

bill would have given the FDA the authority to limit the advertisements to consumers of newly approved drugs, while the Agency is still reviewing the safety concerns of the drug for a period of up to three years. FDA could have restricted DTC ads, only if it determined on a case-by-case basis that additional data about serious risks needed to be compiled after approval and that the public health could not be protected by less restrictive means, like a disclosures statement. This authority fell clearly within the bounds of the first amendment, and I was disappointed that we didn't ultimately hold onto it. The final legislation only included some extremely limited provision and some very loss civil monetary penalties for false and misleading ads. They simply would not give the FDA the tools it needs to address what I think is a very concerning practice.

I want to mention briefly another concern that I have. DTA advertising is a critical issue. It actually represents a relatively small fraction of all drug promotion activities. In fact, I am more concerned about the practice of advertising to physicians. That form of promotion occurs much more frequently and outside of the public view, so it receives less scrutiny by the American public. We know, though, that it is inside the doctors offices where the most persuasive and effective advertising really goes on. Their promotional documents are accompanied by meals for the entire staff, tickets to sporting events, personalized gifts. Obviously, this is a topic for another day, but I do hope that we will have an opportunity to address it soon.

Mr. Chairman, I look forward to the haring. I thank you again for convening us, and I hope this will be a beneficial education for everyone involved.

Mr. STUPAK. Thank you, Mr. Waxman.

We have five votes on the floor. One is a motion to recommit, which will be intervened by a 15-minute vote, so we are going to recess for one hour. Mr. Whitfield said that he will graciously hold his opening statement until then, and we will come back and have Mr. Whitfield's opening statement, and we will have a couple of hours to get through this hearing. So we will be in recess for one hour.

[Recess.]

Mr. STUPAK. The hearing will come to order. When we left for our extended recess, Mr. Whitfield was waiting patiently for his opening statement, and the gentleman will now be recognized for his opening statement.

OPENING STATEMENT OF HON. ED WHITFIELD, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF KENTUCKY

Mr. WHITFIELD. Mr. Chairman, I thank you and I certainly want to thank the witnesses today, and we apologize for the delay, which seems to be not uncommon here in the House.

This obviously is quiet an important hearing that we are having here today, and I do think it is important to reiterate what some other members have said that there is a basic legal principle in the United States about free commercial speech. And I, for one, do not really have a problem with advertisement of medical products on

televisions, because I genuinely believe that one of the problems in our healthcare system today is a lack of information, and I know that one of the members mentioned the fact that for every $1 of advertising that drug companies do on television, there is $6 of revenue for that product, and I think Dr. Burgess touched on the fact we do not know, however, what healthcare dollars have been saved by patients using medicines that may have been advertised on television.

So I think to have just sort of a blanket criticism of advertisement by drug companies is not really accurate, or is not correct. Obviously, we cannot stand for misleading advertising, deliberately misleading the American people, and we do have rules in effect relating to the FDA and ads that are put on television relating to medical care for patients, but as we have this hearing, and we have had others on this subject matter, we will value the input that the witnesses have today because I think the bottom line is the more we have patients talking to their doctors and the more information that patients have, I think that gives us the best opportunity to provide good healthcare. That is, I want to reiterate, once again, we certainly are not going to stand for or put up with or allow misleading advertisement or advertisement that is blatantly incorrect.

So with that, I look forward to our hearing today, Mr. Chairman, and I think this is a very important area for us to continue to look at. Thank you.

Mr. STUPAK. Thank you, Mr. Whitfield. Mr. Barton and Mr. Dingell are going to try to make it. If they do come, we will have them give their opening statements at that time.

But that should conclude the opening statements of the members. Members are back and forth between the health subcommittee, so we will begin with our first panel. Now, the first panel is Dr. Ruth Day, who is director of medical cognition laboratory at Duke University. Dr. Day, would you please come forward? And Dr. Day, it is the policy of this subcommittee to take all testimony under oath. Please be advised that you have the right, under the rules of the House, to be represented by counsel during your testimony. Do you wish to be represented by counsel, Dr. Day?

Ms. DAY. No.

[Witness sworn.]

Mr. STUPAK. Let the record reflect the witness replied in the affirmative. You are now under oath.

By the agreement of both parties, Dr Day is going to have a little extra time for her opening statement. So Dr. Day, we traditionally keep it at 5 minutes, but we are going to extend you a courtesy of a little extra time because of the expertise in which you want to explain to the Committee. So I will let you begin your testimony, doctor.

TESTIMONY OF RUTH S. DAY, PH.D, DIRECTOR, MEDICAL COGNITION LABORATORY, DUKE UNIVERSITY

Ms. DAY. Thank you and good afternoon. My name is Ruth Day. I am a faculty member at Duke University and director of the medical cognition laboratory there. My expertise is in cognitive science, how people understand, remember and use information. I rec-

ommend that everyone consult the screen. I am going to be showing visual displays throughout my testimony.

I am not here today as a naysayer. I am not here to say that direct-to-consumer adverting is bad and should be withdrawn from the market. I am also not here as a yea-sayer. I am not here to say that direct-to-consumer adverting of prescription drugs is good and should be retained. Instead, I am here to report research on how people understand and remember information from these drug ads.

This research was not funded by any drug company, ad agency, advocacy group, or government agency. So the basic question is how do people understand information about drugs. And the answer is with difficulty. And there are many possible reasons for this. There is a very heavy information load. There can be complex and technical information and so forth; however, I am going to focus on the problem of cognitive accessibility.

Cognitive accessibility is the ease with which people can find, understand, remember, and use drug information, and hopefully in a safe and effective manner. Cognitive inaccessibility occurs whenever people have trouble doing any one or more of these things. Research in my lab looks at drug information from a variety of sources, from television to the Internet to hardcopy, and here are just some of the types of information sources that we do study. DTC, or direct-to-consumer, advertising does take place in all of these areas, but today, I am focusing just on our research on the prescription drug ads on television.

Our basic approach and research has three parts. We begin with a cognitive analysis of the ads, so wherever they have come from, in this case television, we obtain quantitative measures of cognitive accessibility and calculate various scores, put them together, and then we compare the cognitive accessibility in the presentation methods for benefits versus risks in particular, and other things as well. We then develop an enhanced version if we think there is a problem, where we enhance the type of information that is disadvantaged, and we retain exactly the same information, but just present it in a way that people are more likely to get it. Then we perform cognitive experiments to test for the effects on attention, comprehension, memory, problem solving, decisionmaking behavior, and when we can, ultimately, health outcomes.

Many cognitive principles underlie this research that are well-known and documented. I have time to only address a few of them today as shown on the screen.

[Slide shown.]

Language difficulty or level, chunking, location, speed, and attention, which I will be describing shortly.

So how do we get these TV ads that we analyze? We have been collecting them since the year 2000, continuously, through today and beyond, and we essentially use the broadcast-capture method. We record on a daily basis, and capture the ads that are embedded in the various programs. Therefore, we do not target specific health conditions or specific drugs; we study all of them.

I am going to start with some of our research from the early years, 2000–2001, and we continue on these today, but just to get us started what our original findings were. Here is the way a typ-

ical experiment goes. We show people a TV ad, and then afterwards, we test them on their knowledge about the benefits and the risks and other types of information. We use a variety of cognitive tasks. I will only have time to, really, tell you about one type of task today. So when we ask people, "well, what is this drug used for," we then plot percent correct, as a function of what drug ad they saw, and here are some early results for three drugs: Paxil, Nasonex, and Orthotricyclen. And the results are good. People know what the drug is used for, ranging from about 70 to 90-plus percent correct. That is good. When we asked for the same ads, and what are the possible side effects that were presented in the ad, performance goes way down. So here we have benefits; here we have risks. So people are not getting this information well at all. Averaging over many experiments on many ads, on average, we were getting about 80 correct on the benefits and about 20 percent on the side effects, with variations across specific ones, of course.

So how are these benefits being presented that enable people to understand and remember them? Well, here is an example where you are told something about a foot-long frank and your grandpop Frank and so on, and so this ad does bring forth the idea of two sources of cholesterol: food and family. And the way the benefits are handled is very effective. Here is a case for Wellbutrin XL, and there are two main messages in the ad, that it treats depression with a low risk of sexual effects. And we find that they repeat the low risk of sexual effects so often that that is almost a stronger message than what the drug is for. Here are other cases where there is great care taken in presenting the benefits. For example in Crestor, the mantra "down with the bad; up with the good" type of cholesterol is very effective. And the others are all effective as well in presenting two concepts, many of which are difficult to understand, and they are getting across and people understand them.

What about the risks? Well, before I show you how the risks are presented and what the consequences are, let us raise this question: why should the public know about risks? Here is a quote. "Drug information should be provided only in such medical terms as are unlikely to be understood by the ordinary individual." And that came out in the U.S. Code of Regulations, 1938, and that was a view that prevailed at that time.

Today, there are people who have viewpoints, both pro and con, as to what and how much consumers should know about the potential risks of drugs. Those on the pro side cite it is important for patients to have informed consent about what they are taking, and understand what it is and then participate in decisionmaking with their physicians. For example, they might try lifestyle changes before going to a medication, or just go forward on the medication. And one I find particularly convincing is that then they would have a better idea of what appropriate action to take should any of these side effects occur. On the con side, some people say if you tell people too much about the risks they will be scared, they can't understand them anyway, maybe they won't comply, and so on. So there are these differing views today, but the balance has swung, very considerably toward the pro side.

So now going back to the original finding that people know a lot about the benefits after an ad and not much about the side effects,

why is this so hard? There are many possible reasons, such as this fear idea, their motivation, education, health literacy, and so on.

So let's see how we look at what is going on here. When we capture an ad, one of the first things that we do is to get a transcript, and by this, I mean the soundtrack, the spoken transcript by the voiceover or the characters on the screen, and we look at all of it, but we focus primarily on the benefits and the risks. So let's look at the language level that is used. There are many linguist measures that we use in our research, some of them complex, from word selection and grammatical structure, logical structure, cohesion, readability measure, and so on, but all of them speak to comprehensibility, how easy would it be to understand.

Here is one of our first studies from 2001, 29 drug ads, and if you look, averaging across all of them, what grade level of comprehension would a person need in order to understand the benefits is about a sixth-grade grade level. That is pretty good for a general population. What grade level of comprehension would they need in order to understand the side effects is about a ninth-grade level, so that is three grade levels higher in order to understand the side effects as opposed to the benefits, so that is what part of the problem is. And this is an average across many ads. Some are even more extreme than shown here. One we collected that you had to have eight grade levels higher to understand the side effects, but of course not all of them show this pattern, and some are more equally balanced.

So now, let's look at a speaker timeline for a drug.

[Slide shown.]

The yellow boxes show when someone is speaking and just the straight black lines are when there is some silence, and there is time going from left to right. All right, this is a particular ad for Allegra, and it started out in the first yellow box, and it said it is allergy season or Allegra season. And then there was a pause, and then there was a message, again a positive message, and a pause, and then there was a long block where it started by talking about what the side effects were and went immediately into other information, so the point about this display is that for the first blocks of information, there is what we call chunking. You put together a set of information, and then you separate it from surrounding information, in this case with silence, and that helps mental digestion, so to speak. Whereas, in the long block, after you say the side effects, if you keep talking, there is less opportunity for that to happen. So that is a case where the side effects are being disadvantaged in that criterion.

Let us talk about location of information. There is a well-known phenomenon in the memory literature about what happens if you present a list of things for people to remember, whether they are words or number of whatever, when you then plot percent correct as a function of the location of the items in the list, this typical finding comes out, and this has been repeated time and time again. This is a well-known phenomenon. People remember the information better at the end of the list and the beginning of the list and have trouble with the information in the middle, and it is in the middle and a little bit past the middle, so on the screen, in the middle and toward the right, so to speak.

So now, let us use this to ask the question, where is the location of side effects in, say, this group of ads that we captured? We are going to look, for each ad, where, in time, were the side effects presented. So we are looking at location as a function of elapsed time. And there are the results. The pink bars are just for each drug, and I have put a box around to show that it is approximately 60 to 85 percent of the time elapsed when the side effects come in. When we combine all risks, and risks include not only side effects, but contraindications, who should not take a drug, interactions with other drugs, and so forth, you will see that exactly the worst location is being used for this negative information about the possible risks of the drugs. So clearly, the risks are being presented in an unfavorable location, but you might say what effect does location have on cognition? For mental processing we need evidence.

So we produced our own little TV ad for a hypothetical drug called Flu-Aid, and its structure and content is exactly like typical drug ads, and our purpose is to vary specific factors to observe effects on cognition. And so people would see the ad, and on a random basis, half of them would hear the side effects in the usual unfavorable location and/or in a more favorable location with the exact same visual and auditory information. They differ only in the location of where the side effects are presented.

We are now going to plot percent-correct side effects for those two locations, and people who received the information in the unfavorable location did not do well. People who received it in a more favorable location did very well. In fact, there is a 100 percent increase in what they knew right after the ad. There were still some people who were unable to report any side effects at all, but virtually of them, nearly all of them, had had the ad with the information in the unfavorable location—a big difference there.

Let us now talk about speed. There are two interesting ads from 2005, both for sleep medications Ambien and Lunesta, where there were some interesting variations in speed of speaking during the ad, so we counted the speed of speaking, in terms of syllables per second, and here for the Ambien ad, there was a speed up when the information came for the side effects, whereas the Lunesta, there was no speed up. And so we did an experiment with both of these ads. We are focusing just on the speed, now, of the side effects, which Ambien being twice as fast, approximately, than Lunesta. And you could still say, so what? Just because it speeds up, does speed effect knowledge that people take away, and the answer is, yes, indeed. So the faster they spoke, the less that people took away.

The final one is about attention, and for this I am going to be relying on an ad campaign that started in 2005 and continues today for Nasonex. This is the Nasonex bee, a very charming character with a foreign accent, very appealing. And we were testing this in the laboratory, and we found people weren't remembering the side effects at all. And we were wondering about this. It only had five side effects, and the limits of short-term memory are approximately seven, plus or minus two, so it is well within that, but it was particularly low. And when we analyzed the ad, we found that there was some interesting visual effects going on during the speaking of the side effects. So instead of showing you the video,

I have some stop-action shots of what the bee does here. So if you will fix your attention on where the red arrows are on his wings, I will now show you some screenshots, and watch what happens.

[Slide shown.]

Did you see how the wings moved and also flashed? That was going on during the side effects. Right afterwards, there was a section on benefits, and during this point, this part, the bee was hovering, and you could barely see his wings at all, during the expression of the benefits at the end of the ad. So we counted the number of wing flaps per second for the benefits section versus the side effects that I have described and found that there were many more wing flaps going on during the side effects section, and there were also some flashing effects going on—might have been graphic art effects—and these were all going on during the side effects and very little light during the benefits. So all of these wing flaps and wing flashes and sparkly things essentially divided the attention of the viewers. Instead of concentrating on the auditory channel where the side effects were being presented, they were pulled away to the visual channel, and thus led to decreased knowledge, and there were many more comments from this particular ad that there weren't any side effects. People actually denied—they didn't say any.

And I first presented these results at an FDA public meeting on direct-to-consumer advertising in November of '05, and early in '06, there were new versions of this ad. In one, during the side effects, the bee had soft, black wings. In another, he was just hovering, and you couldn't see any wing action much at all. In another there was no bee at all. And so we did a head-to-head comparison in a laboratory experiment between the original wing flap ad and the hover ad and looked at how much people knew about the side effects, and as you can see, everything else was the same, the side effects and so on, but they got much more of a take-away message about the side effects from the hover ad. So this is an example of visual distraction, only one of many techniques that can be used.

So to go back to the original question, why is it hard for people to get the information about risks, and particularly side effects, many of these cognitive principals, only few of which I have been able to talk with you about today, are indeed responsible, and we have tested them experimentally in the lab.

So here are some conclusions. There is currently, and has been for a long time, an unfair balance between the presentation of the risks and the benefits in these ads. Now, when I say unfair balance, I mean in terms of the cognitive accessibility, the presentation techniques that make it easier or harder for people to get the information. I am not talking about fair balance, as the FDA does, as to what is in the ad. The business of what is in the ad is the company's and the FDA. What I am talking about is given what is in the ad, how cognitively accessible is it to the viewer. So since the year 2000, as we reported many of the results, there have been changes, and many of them have been addressed to our particular results in some ads, but there certainly need to be many more.

Otherwise, we are in the following situation: that the ads are pressing risk information, they are physically present, but function-

ally absent. What is the good of having information that is physically present versus functionally absent? It fulfills certain legal requirements, but it is not communicated to the intended audience.

So some recommendations: we need to have an evidence-based approach in evaluating these ads, to be used by industry and the regulators as well, using the same criteria. So say for example, for location and speed and other things, to have a checklist with the same quantities measure, and make sure that the treatment of benefits is as good as the treatment for the risks—they are roughly balanced, and then we can get into fair balance of the cognitive accessibility of both types of information. Otherwise, here is the final point, risks go like this: we send them out the viewer, and they go up over their head and gone. But I think we can this information into the head, and in order to do it, we need to increase cognitive accessibility.

This concludes the formal presentation of my testimony. But Mr. Chairman, I would like to comment that at the House request, I have examined ads for the hearing, and if you would like that commentary now, I will do it.

Mr. STUPAK. If you would, do so quickly.

Ms. DAY. OK, very quickly, we were able to conduct full experiments on two of the ads, and I will show you. For the Lipitor ad, here is the same set of results for how well they did in getting the benefits versus the risks, the same kind of pattern. For the benefits, one benefit came across much better, the lowering of the cholesterol, than of reducing the risk of heart attack, and for the side effects, neither came across well, that there could be muscle pain or weakness. And I do not think it is the fault of this ad. I think it is the problem with the statins in general. This is a very serious side effect that can occur with the statin drugs, but when you say muscle pain and weakness, these are things that the public has experienced many times, and they don't understand how serious, taken together, they can be.

And there was another thing in here that all of the statin ads tend to have something like: you need simple blood tests to check for liver problems. And we asked people are there any medical tests you should have, and they did pretty well. Most said yes, but when we asked what are they for, they really didn't know. Most said they didn't know; some said liver tests, and then I didn't even list all of the others. They are all over the place.

So when we asked people when should these tests take place, nearly all of them said before you take the drug. It qualifies you to take the drug. So there is no sense that certain drugs can effect liver function and other function while taking them or that the test might be a monitoring later on, so that is general thing where we need some public education about what it means when these statements are made.

The other one that we were able to do testing on is Procrit, and there is its profile in terms of what people could report about the benefits and risks, a little bit more in balance here, and both of the messages came across strongly, that it does something for red blood cells and also your energy level and so forth. And there was something interesting about side effects, that one they got, the one about diarrhea, but not the other one because it was called edema,

and I don't think the general public knows that edema means swelling. So this is just a simple case that had they used the term swelling, they probably would have done much better.

That concludes my review of those ads.

[The prepared statement of Ms. Day follows:]

Testimony to the U.S. Congress, May 8, 2008.
House Committee on Energy and Commerce,
Subcommittee on Oversight and Investigations

Direct-to-Consumer Drug Ads: What Do People Understand and Remember?

Ruth S. Day[1]
Duke University

Introduction

I am a faculty member at Duke University and Director of the Medical Cognition Laboratory. My expertise is in cognitive science – studying how people understand, remember, and use information.

I am not here today:
--to be a nay-sayer – to say that DTC ads are bad and should be withdrawn from the market.
I am not here today:
--to be a yea-sayer – to say that DTC ads are good and should be kept on the market.
Instead, I am here:
--to report research on how people understand and remember information in DTC ads.

This research has not been funded by any pharmaceutical company, advertising agency, advocacy group, or government agency.

Basic Question

The basic question is – How do people understand drug information?
The answer is – with difficulty.

There are many possible reasons for this difficulty – for example, there can be a heavy information load, complex and technical information, and so forth.

However our focus today is on "cognitive accessibility."
"Cognitive accessibility" is the ease with which people can find, understand, remember, and use drug information, and do so in a safe and effective manner (Day, 2006). Cognitive in-accessibility occurs whenever people have trouble with any one or more of these processes.

Research Approach

Research in my lab examines a wide variety of drug information sources including television, the internet, and hardcopy. DTC occurs in all these environments, but today the focus is on television ads for prescription (Rx) drugs.

The basic research approach has three phases.

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[1] Box 90086 / Duke University / Durham, NC 27708-0086 / ruthday@duke.edu

In the Cognitive Analysis Phase, we obtain quantitative measures about how information is provided, calculate cognitive accessibility scores, and compare the cognitive accessibility of information about benefits vs. risks.

In the Enhanced Display Phase, we keep the same information, but provide it in more cognitively accessible ways, based on well-established cognitive principles.

In the Test Phase, we perform cognitive experiments to test the effects of the Original and Enhanced versions on various cognitive processes such as attention, memory, comprehension, problem solving, decision making, behavior, and ultimately health outcomes.

Many cognitive principles underlie this work, including various language properties, chunking of information, location of information, speaking speed, and divided attention, as I'll describe shortly.

We have been collecting television ads for prescription drugs continuously since the year 2000. We record several hours from broadcast channels on a daily basis, then extract the prescription drug ads that occurred. Therefore we do not "target" any specific health conditions or drugs – we study all of them.

Major Finding

In a typical experiment, research participants view an ad (or multiple ads), then complete a series of cognitive tasks that examine their attention, comprehension, memory, and/or problem solving. A major finding concerns what happens when we ask them to report benefits (e.g., what the drug is used for) vs. what the possible side effects are (a type of risk). They are asked to answer based only on what was in the ad, not any prior knowledge they might have. People do much better in reporting the benefits than the side effects, as shown in Figure 1.

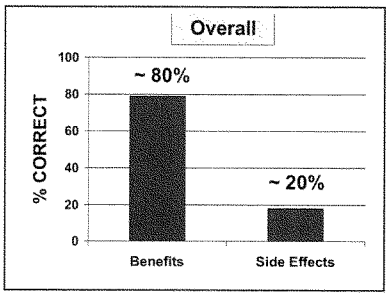

Figure 1 – Percent correct free report for benefits vs. side effects (averaged across multiple experiments).

Why should consumers know about risks? There are many views about this question. For example, the 1938 U.S. Federal Regulations says that, **"Drug [information] should be [provided] only in such medical terms as are not likely to be understood by the ordinary individual."** Today some stakeholders argue that providing too much risk information could be harmful – it could frighten or confuse patients, decreasing chances that they will comply with prescribed medical treatment. Others argue that consumers have a right to know what side effects might occur, so they can discuss treatment options with their physicians, take drugs in a safe manner, and know what action to take if any side effects occur.

Presentation of Benefits vs. Risks in Rx TV Ads

Benefits

The cognitive accessibility of benefits is generally high in Rx TV ads. For example, more time is devoted to them, the name of the drug and its benefits are usually repeated multiple times, and the language used to express them is usually easy to understand. Sometimes even complex concepts are provided in easy-to-understand ways, such as the role of food and genetics in affecting cholesterol levels, that a given drug affects both "good" and "bad" cholesterol in helpful ways, or that a given drug contains two drugs to treat two health conditions at the same time.

Risks

The cognitive accessibility of risks is generally low in most ads. For example, the information is often presented using more difficult-to-understand language, without "chunking" key information (separating it from surrounding information with pauses), providing it in unfavorable locations, using a faster speech rate, and/or providing visual or auditory distractions at the same time.

Sample Experiments

Examples of these cognitive accessibility factors and how they affect cognition are shown in the next slides.

Insert slides here

Conclusions

Overall, side effects and other risks are disadvantaged relative to benefits – the techniques used to present them often render them lower in cognitive accessibility. Although these cognitive accessibility problems are widespread, not all ads have them. This research shows that people have trouble understanding and remembering drug risks; however they improve when appropriate cognitive accessibility principles are used in the ads. For example, laboratory experiments show that viewing a given ad with speed-up of the spoken side effects makes it hard to remember what they were, while the same ad with no speed-up yields better performance.

Since these results were first reported, there have been some positive changes in some ads, for some cognitive accessibility factors. However many more are needed. Otherwise, risk information will continue to be **physically present but functionally absent** in many ads.

Recommendations

An evidence-based approach is needed (for both industry and regulators) to evaluate ads in terms of cognitive accessibility factors such as those described here. Separate analyses of benefits and risks are needed, to ensure that there are no major discrepancies in their cognitive accessibility. Ads with unfavorable cognitive accessibility scores – known to decrease comprehension and memory – could then be modified; in some cases additional cognitive testing may be useful. If done prior to airing, this approach could save considerable time and provide ads that are more useful to consumers.

Reference

Day, R.S. (2006) Comprehension of prescription drug information: Overview of a research program. *Proceedings of the American Association for Artificial Intelligence, Argumentation for Consumer Healthcare. aaai.org.*

Mr. STUPAK. I thank you, doctor. Before we go to questions, Mr. Dingell, would you wish to make an opening statement, sir?

Mr. DINGELL. Mr. Chairman, I won't impose upon the Committee by submitting an opening statement in so many words. I will ask unanimous consent that I be permitted to insert that in the record in the appropriate place and fashion, and I thank you again for your courtesy, but also commend you for your vigor and your energy in conducting this. And while I am at it, to the witness, Dr. Day, thank you for your very fine presentation.

[The prepared statement of Mr. Dingell follows:]

STATEMENT OF HON. JOHN D. DINGELL

Mr. Chairman, thank you for holding this important hearing on the risks of direct-to-consumer advertising of drugs.

In the wake of revelations concerning the safety problems surrounding widely advertised drugs such as Vioxx and Ketek, we must ask how well the policies that govern direct-to-consumer advertising are serving the American people. Direct-to-consumer or ″DTC″ advertising of new drugs has been particularly problematic for new drugs that may lack a broad safety record.

About 10 years ago, the Food and Drug Administration (FDA) relaxed its rules for direct-to-consumer advertisements of prescription drugs, making the U.S. one of only two countries in the world that allow such marketing. Since then, Americans have witnessed a flood of DTC ads, particularly on television.

In fact, spending by drug companies on DTC ads has grown exponentially since 1999. And it is no wonder-research shows that for every $1 spent on DTC advertising, up to a $6 increase in drug sales result.

The drug industry asserts that these drug ads benefit the public health by educating both consumers and physicians about disease and potential drug therapies. As we explore the risks and benefits of DTC advertising, however, it is worth noting the words of a former New England Journal of Medicine editor who said drug companies were ″no more in the business of educating the public than a beer company is in the business of educating people about alcoholism.″

Nevertheless, drug advertising can indeed serve an educational role, provided drug companies scrupulously adhere to FDA guidelines for DTC ads. FDA guidelines and regulations require that direct-to-consumer ads must:

- be accurate and not misleading;
- make claims only when supported by substantial evidence;
- reflect balance between risks and benefits; and
- be consistent with FDA-approved labeling.

Regrettably, investigations by this Committee have revealed systematic violations of these principles by a number of drug companies. Some ad campaigns have been misleading and others appear downright deceptive.

DTC advertisements may well serve an educational purpose, but they are primarily designed to sell products.

The Food and Drug Administration shares the responsibility with pharmaceutical companies to ensure that drugs are accurately marketed to consumers. And Congress must ensure FDA has the authority and resources to effectively monitor whether drug companies are properly marketing their products in compliance with the law.

Mr. Chairman, I commend you and your Subcommittee for today's hearing on direct-to-consumer advertisements and I look forward to the testimony of each witness.

Ms. DAY. Thank you.

Mr. STUPAK. Thank you, Mr. Dingell.

OK, we will start with questions, and I will begin the questioning. Doctor, the techniques you described, did you get them from any psychology textbook or from an advertising manual?

Ms. DAY. All of them are from textbooks in cognitive psychology and cognitive science. That is where the research has been con-

ducted. I don't know if they are in the marketing. I do know many of them are in marketing textbooks, but not all of them.

Mr. STUPAK. OK, does the actual number of benefits and the number of side effects affect your research? For example, if a drug has two benefits but seven side effects, wouldn't there be more side effects to forget?

Ms. DAY. Yes, that is a good point. We take care of that by the following. If you recall the first slide that I showed, which were for three drugs, and I showed how poor the recall was for all of the side effects, they vary widely in terms of the number of side effects, three, seven, or nine, and the results were all the same, so in that experiment, there was no difference. In the two studies that I just mentioned now for Lipitor and Procrit, they were equally balanced. Each had two benefits, each had two side effects, and as you can see, the results showed the same pattern.

I would just comment on the Lipitor ad if I might, it says that there are the two side effects. You might consider liver problems as an implicit side effect, but it is not explicitly stated as such, so we do study memory load and find that is not driving our results.

Mr. STUPAK. You study all commercials, not direct-to-consumer ads, right?

Ms. DAY. No, we are not an advertising outfit. We study all drug information. We will study pharmacy leaflets. We will study medication guides. We will study the full prescribing information that the physicians use and that is the approval document——

Mr. STUPAK. Well, let me ask you this. If you do all of these studies on pamphlets and ads and anything else, are there good ads? I mean ones that do a good job of both presenting the risks and benefits in a way that people truly understand and remember them?

Ms. DAY. I would not do a categorical statement that some ads are good and some ads are bad or wrong, but I can speak to some ads that are particularly good in certain features.

For example, in connection with the speed-up ads, when I first saw the recent campaign on Enablex, for bladder problems, I was absolutely stunned at how slowly the entire ad is spoken, and there is absolutely no speed up for the side effects, and we have recently tested that ad and people do very well with it.

Mr. STUPAK. Well, let me ask you this: if an ad agency or drug company wanted to make sure that the consumers actually receive the information they are supposed to receive from an ad, is there a way to test for it?

Ms. DAY. Absolutely. Just as we have done here, it could be included in their market research that they do. Market research is usually designed to find out if there is brand awareness and the messages and appeal of the people speaking, but some of ours are full experiments that I haven't talked about here today, but some of the simple things that we do can easily be combined in their market research endeavors.

Mr. STUPAK. Have you or your group there at Duke University ever been approached by a drug company or an ad agency or the FDA to assist them in analyzing ads to make sure they are fair?

Ms. DAY. Well, I have never been approached by an ad agency, period. I have been approached by drug companies to help them with their campaigns, and I have not done so. I have been approached by the FDA to give public testimony in various hearings on direct-to-consumer advertising, and I have done that. And in those meetings and in other professional meetings, such as the Drug Information Association, there is a wide variety of stakeholders, and I have spoken informally with everyone about my research and the techniques, but I have not consulted on any specific ads or ad campaigns that anyone has.

Mr. STUPAK. Well, would testing an ad to make sure that people actually understood the ad or the information in the ad, would that take a lot of time and money to do?

Ms. DAY. Well, a full battery of what we do on an ad like this is about 30 to 40 minutes, including the informed consent and so on. We get a lot more than what I have talked with you about today. But for just what I have talked with you about today, it could take about 15 minutes. As for the money, the money would be very nice to be able to fund this. We would be able to study a lot more ads. We are doing this ourselves on a shoestring, but we study a wide variety of individuals of all educational levels and backgrounds, and we study physicians as well as the consumers, and we find that the physicians have the same kind of trouble with the written information about the risks, as opposed to the benefits, as the consumers do. But we don't have sufficient funding to do as much as a national look from our laboratory across many consumer groups, and I think the companies would have the funding to do that.

Mr. STUPAK. Let me ask you another question. There is a lot of interest of this hearing on the floor from members, and when we were down voting for over an hour, a number of members mentioned it, and one member asked me in particular to ask you this question. Congressman John Hall from New York wanted to know the affect of these ads on children, the cognitive accessibility, do you find it different with age? He objects to the erectile dysfunction ads going during children hour, or the going problem, and all of these other things are ones that he pointed out in particular. Do kids pick up on these?

Ms. DAY. All of our research is with people age 18 and over. However, it is interesting that when, after the direct-to-consumer advertising effects came to the public light, around the time of the COX2 inhibitor hearings, the Vioxx and so on, there was attention drawn to direct-to-consumer advertising, Pharma, the Pharmacological Trade Association, did draw up a code of operation, and I believe at that time, those types of ads, for ED, were going to be aired after the 10:00 hour, when the family hour is over. But they are now during the evening hours, so something there has changed, and I have anecdotal reports I have heard from colleagues, but we have not done research about this.

Mr. STUPAK. You mentioned that in one of the drugs that you looked at, it actually revealed that there was an eight grade level difference between the risks and the benefits. That is a large swing in your study, and that was for the Flovent inhaler, wasn't it?

Ms. DAY. I did not show that here today. That was a long time ago, and there were quite a few that had a sixth grade difference as well. And I believe it is my responsibly to follow those ads over time and see if those things are corrected after they are reported, and I have not done that yet, so I can't answer.

Mr. STUPAK. It was Flovent, and it was eventually pulled from the market.

Ms. DAY. Right, it was.

Mr. STUPAK. Mr. Whitfield for questions, please.

Mr. WHITFIELD. Thank you, Mr. Chairman. And Dr. Day, thank you for being with us today.

The medical cognition laboratory at Duke, how old is that laboratory?

Ms. DAY. Well, this is a part of my own laboratory, and I have been doing research on this since about the mid-80s. The first published account was in 1988.

Mr. WHITFIELD. You said part of your laboratory?

Ms. DAY. Yes, my laboratory also looks at courtroom cognition, how judges and jurors understand and remember information about laws and apply them to decisionmaking. So most of the laboratory now is devoted to medical cognition, but we do have other projects as well.

Mr. WHITFIELD. And you are part of Duke University and you are the director of that laboratory?

Ms. DAY. Yes, I am.

Mr. WHITFIELD. And the only funding is through Duke University.

Ms. DAY. That is correct, and my own pocket and my own time. I have received no funding, personally, for this.

Mr. WHITFIELD. And I know, in your opening statement, you said that you are not saying that direct-to-consumer ads are bad and should be withdrawn. Is that correct?

Ms. DAY. That is correct, and I am not saying they are good and should be retained.

Mr. WHITFIELD. And you are not saying they are good and should not be withdrawn.

Ms. DAY. Right, I am looking at what people get from the information and how we can do things to enable them to get more.

Mr. WHITFIELD. And I agree with you. I mean I think the more information patients have, the better. One part of your cognitive accessibility study which seems to be missing to me, which is a vital and very important part, and I don't know if you have studied it or not, but obviously before any patient can use any of these medicines that we are talking about, they have to have a prescription, and they have to have a consultation with their physicians, and I am assuming that the physician also has the responsibility to talk about benefits and side effects.

Ms. DAY. That is correct.

Mr. WHITFIELD. Have you ever studied that aspect to take this one step further?

Ms. DAY. And by the way, pharmacists also have a responsibility to discuss this with the patients as well. I have studied physicians, not for the direct-to-consumer ads, because they tend not to like those anyway. But I have studied them in the written information

from company Web sites, so I have taken exactly the side effects section from drugs and shown them to physicians, either in the original form or in an enhanced version that I have developed for showing side effects, and they have studied them and then reported. And in his particular case that I am thinking of now, it was for a drug that they all regularly prescribed, because this was at a medical convention or meeting where I knew what their specialty was. And they did a very poor job in reporting what those side effects were afterwards when the information was presented in a traditional way with sentences and bullets. However, when I presented it in a way that is more graphic in design, that emphasizes severity of the different side effects, they improved dramatically. There was no difference between the physicians and the laypersons in this.

Mr. WHITFIELD. I think that is an important part to the point that we need to make. I think many of us would be really concerned about ad if patients looked at those ads and then they went to the drug store and said I want this. But they can't it without a prescription.

The second point I would like to make, have you ever submitted your research studies that you discussed in your testimony to a peer-reviewed journal?

Ms. DAY. Yes, I have. A related work, not the details of today, was in the Psychology of Learning and Motivation, the first one in this line. And another was to the American Association for Artificial Intelligence. That was a juried selection.

Mr. WHITFIELD. And how many other laboratories similar to yours are there with other universities around the country?

Ms. DAY. I am not really sure. I know of clusters of people who do research on all of this, and sometimes they have a wider or narrower focus on certain issues.

Mr. WHITFIELD. And do you all get together periodically for——

Ms. DAY. No, I think we should, but we wind up together at different meetings, and I am thinking of convening a conference to bring people together to talk about these issues.

Mr. WHITFIELD. Drug companies are required to include information about risks as well as benefits. How does a drug company or the FDA draw the line when communicating risk information? Is there a point when an ad can include too much information on risk and viewers begin to tune out the information?

Ms. DAY. Two answers to that: first of all, it is not for me to say how many can or should be there based on the available information about the drugs, and I commented on that before. That is the business of the FDA and the companies. But I think your question is about how much information is too much. You are talking about information load. And we have found that it is not how much information is presented, but how it is presented. So to go back to this last example with the physician looking for Avandia and as we took it off the company Web site for the patient information section. There were 26 side effects. No one can remember all 26, obviously, but when we gave them to people and they tried to recall, they could get very few, six or seven, when we gave the original form of the information. But when we gave it to them in the enhanced version, they went up dramatically, and it depended upon what

cognitive task we used. When we asked them a number estimation task about how many were there, people went up to perfect performance. So it isn't how much information you give. It is how you give it.

Mr. WHITFIELD. I would just ask one brief question. Does anyone purchase your test results from the laboratory?

Ms. DAY. No one, not from me. I do not earn any money.

Mr. WHITFIELD. So no one really has access to it. You don't give to any groups?

Ms. DAY. No, no one has ever requested it. We have found that somebody came as a test subject, and we found out later works for one of the companies, but no.

Mr. STUPAK. If I may, just a little follow-up on Mr. Whitfield's questions. The most important part of your testimony, if I could summarize it, it is not so much what is presented in the ad but what people take away from the ad.

Ms. DAY. Well, I would say there is an intervening step. It is no so much what is in it, but how it is presented benefits what they will take away, so that you can be in legal compliance with FDA regulations as to what needs to be in there, but if you present it in a certain way, you are really decreasing the chances that people are going to walk away with it, and conversely.

Mr. STUPAK. So conversely is presentation will determine what people take away from the ad?

Ms. DAY. Yes, and I am saying not presentation in terms of cutesy things going on and so forth, but taking into account well-known and well-documented cognitive principles.

Mr. STUPAK. Any further questions? Having no further questions, thank you, and thank you Dr. Day for your testimony.

I would now call up our second panel of witnesses. On our second panel, we have Dr. Edward Langston, who is chair of the American Medical Association's Board of Trustees, Dr. Mollyann Brodie, who is Vice President and Director of Public Opinion and Media Research at the Kaiser Family Foundation, and Dr. Marcia Crosse, who is Director of the Health Care Division at the Government Accountability Office. All right, I guess there is a change in the lineup here. Instead of Dr. Ed Langston, we have Dr. Nancy Nielsen who is President-Elect of the American Medical Association. It is the policy of this committee to take all testimony under oath. Please be advised witnesses have the right under the Rules of the House to be represented by counsel. Do any of our three witnesses, our three doctors here, wish to be represented by counsel? OK, you all are shaking your head, so therefore, I will ask you to stand and raise your right hand and take the oath.

[Witnesses sworn.]

Each witness is now under oath. We will now hear a prepared five-minute opening statement from each witness. You may submit a longer statement for inclusion in the hearing record.

Dr. Nielsen, shall we start with you, please, from the American Medical Association. Thank you for being here. If you would, start your testimony.

STATEMENT OF NANCY H. NIELSEN, M.D., PH.D., PRESIDENT-ELECT, AMERICAN MEDICAL ASSOCIATION

Dr. NIELSEN. Thank you, Chairman Stupak and Representative Whitfield, and to the rest of the Committee, thank you for holding this hearing. My name is Nancy Nielsen, and I am clinical professor of medicine and senior associate dean at the University of Buffalo School of Medicine. I am here today as president-elect of the American Medical Association. The AMA welcomes the opportunity to share our policy as well as the House of Medicine's perspective on DTCA's impact on the patient-physician relationship, on its adequacy as a source of information for patients, and its role in driving healthcare costs.

DTCA has become ubiquitous over a very short period of time. According to a recent consumer survey, almost 91 percent of Americans have seen or heard DCTA. The sheer volume that now appears on television in particular, including ads for drugs to treat conditions like erectile dysfunction, raises questions about the timing and the appropriateness of these advertisements for some consumers such as children. Just before 9:00 a.m. this past Easter Sunday morning, while home with a sick grandchild, an ad appeared on TV advertising one of the drugs for erectile dysfunction. I quickly made hot chocolate.

Equally troubling, there is mounting evidence that many of the television direct-to-consumer ads lack fair balance and include claims of benefits that overwhelm risk information, and you just heard a very erudite testimony on that regard. Also, intense advertising for newly approved drugs can exacerbate significant safety problems. The Vioxx case is illustrative of that issue.

The AMA has been and continues to be concerned about the possible negative impact of DTCA on the patient-physician relationship and on patient safety. We are also increasingly concerned about the role the DTCA plays in fueling the increase in healthcare costs. It is all the more urgent now, as Congress grapples with escalating costs, and the need to prioritize limited healthcare dollars.

DTCA has been a lightening rod of concern of our member physicians for over 20 years. Our policy on DTCA has evolved over this period, and the current policy we have submitted to you was adopted in 2006. Product-specific advertisements are considered acceptable if they satisfy the AMA's guidelines, and key points from these guidelines are seven. First, the DTCA should be indication specific and enhance consumer education about both a drug and a disease. Two, should provide a clear, accurate, and responsible educational message. The information about benefits should reflect the true efficacy of a drug as determined by clinical trials leading to FDA approval. Three, it should not encourage self-diagnosis or self-treatment, which of course is not the same as encouraging patients to report symptoms. That we obviously favor. Four, it should exhibit a fair balance between benefit and risk, and again, you have just heard a better analysis of that than I can give you. We certainly believe that the time and space devoted to the benefit and risk information and the ease with which people can find, understand, remember, and use the information about benefits and risks should be comparable. Five, it should present risk information that will be understood by a majority of consumers without using strategies de-

signed to minimize risks or distract from them, as you have just seen. Six, it should not use an actor who portrays a physician or an actual physician to endorse the drug product, unless there is a prominent disclaimer or disclosure. And seven, it should be targeted for placement so as to avoid audiences, like my grandson, that are not age appropriate for the messages presented.

In addition to those guidelines, the following key points from our policy deserve mention. Our AMA supports both FDA pre-review and pre-approval of DTCA prior to broadcast or publication. DTCA for new drugs should not be run until physicians have been appropriately educated about the drug. The length of this moratorium on DTCA could vary from drug to drug and should be determined by the FDA in negotiations with the manufacturer. AMA encourages further research on the effects of DTCA, and we support Congress authorizing ARC to perform periodic, evidence-based reviews to determine the impact on health outcomes and public health. If DTCA is found to have a negative impact on either of these, then Congress should consider legislation to increase DTCA regulation or possibly ban it in some or all media.

In conclusion, recent events have heightened our concern, and the AMA looks forward to working with you to ensure that consumers receive information that is accurate, informative, promotes communication between patients and physician and does not drive inappropriate costs. Thank you very much for the opportunity to be here.

[The prepared statement of Dr. Nielsen follows:]



Statement

of the

American Medical Association

to the

Oversight and Investigation Subcommittee
Energy and Commerce Committee
U.S. House of Representatives

RE: Direct-to-Consumer Advertising: Marketing, Education or Deception?

Presented by: Nancy H. Nielsen, MD, PhD

May 8, 2008

American Medical Association Division of Legislative Counsel
25 Massachusetts Ave. N.W. Suite 600 Washington, DC 20001
(202) 789-7426 www.ama-assn.org

U.S. House of Representatives
Committee Energy and Commerce, Subcommittee on Oversight and Investigations

Direct-to-Consumer Advertising: Marketing, Education or Deception?
May 8, 2008

American Medical Association
Presented by: Nancy H. Nielsen, MD, PhD, AMA President Elect

Direct-to-consumer advertising (DTCA) has become ubiquitous and neither regulatory oversight nor research on its impact have kept pace. As a result, the American Medical Association (AMA) has serious concerns that DTCA is neither balanced nor educational, may adversely affect physician-patient relationships, and contributes to rising health care costs. AMA policy does not oppose "product specific" DTCA if it complies with AMA guidelines. DTC ads must:

- Be indication-specific and enhance consumer education about both the drug and disease.
- Provide a clear, accurate, and responsible educational message.
- Not encourage self-diagnosis or self-treatment.
- Exhibit fair balance between benefit and risk information.
- Present risk information that will be understood by a majority of consumers.
- Not use an actor who portrays a physician, or an actual physician to endorse the drug product, unless there is a prominent disclaimer or disclosure.
- Be targeted for placement so as to avoid audiences that are not age appropriate for the messages presented.

The AMA also supports FDA review and approval of all DTC ads and adequate funding to perform these activities. In addition, the AMA supports a moratorium on DTCA for new drugs until physicians have been appropriately educated about the drug. The length of this moratorium may vary from drug to drug, and should be determined by FDA in negotiations with the manufacturer.

Statement

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Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
United States House of Representatives

RE: Direct-to-Consumer Advertising: Marketing, Education or Deception?

Presented by: Nancy H. Nielsen, MD, PhD

May 8, 2008

The American Medical Association (AMA) appreciates the opportunity to provide its views regarding the role of direct-to-consumer advertising (DTCA) in health care. We commend Chairman Stupak , Ranking Member Shimkus, and members of the Subcommittee for convening this hearing. My name is Nancy H. Nielsen, MD, PhD, an internist and President-Elect of the AMA. I am also a clinical professor of medicine and senior associate dean for medical education at the State University of New York at Buffalo School of Medicine and Biomedical Sciences. We look forward to sharing our policy concerning DTCA as well as our perspective on DTCA's impact on the patient-physician relationship, its adequacy as a source of information for patients, and its role in driving health care costs and utilization.

Background

DTCA has become ubiquitous over a very short period of time. According to a recent consumer survey, almost all Americans (91 percent) have seen or heard DTCA.[i] In under ten years, between 1993 and 2002, the percentage of people who reported that they had seen an ad for a prescription drug on television or heard one on the radio more than doubled.[ii] Nearly a third (32 percent) of Americans have talked to a physician about a prescription drug they saw advertised.[iii]

The foregoing is not surprising since the growth in spending on DTCA between 1989 and 2004 has been explosive. In 1989, the pharmaceutical industry spent only $12 million on DTCA,[iv] and by 2004 spending had dramatically climbed to approximately $4.45 billion.[v] Pharmaceutical companies have increased spending on DTCA faster than they have increased spending on research and development.[vi] Between 1997 and 2001, spending on DTCA increased 145 percent, while research and development spending increased only 59 percent.[vii] Spending on DTCA grew at an average annual rate of 14.3 percent from 2002 to 2005.[viii]

The sheer frequency and volume of DTCA that now appears on television in particular, including ads for drugs to treat conditions such as erectile dysfunction, has raised questions about the appropriateness of these ads for some consumers, such as children. There is growing concern that many of the television DTC ads lack fair balance; i.e., claims of benefit overwhelm risk information presented in the ads.[ix] This can result in trivialization of the safety risks of prescription drugs. Also, intense advertising for newly

approved drugs with limited safety profiles could potentially lead to significant safety problems.[x] The rofecoxib (Vioxx) case is illustrative of this concern.

The AMA has been, and continues to be, concerned about the possible negative impact of DTCA on the patient-physician relationship, patient safety, and is increasingly concerned about the role that DTCA plays in fueling the increase in health care costs. It is all the more urgent now as Congress grapples with escalating costs and the need to prioritize scarce health care dollars. There is growing alarm that DTCA increases utilization of new and more expensive drugs that all too often have limited safety profiles. The AMA does not believe that the Food and Drug Administration (FDA) has adequate resources to carry out its enforcement role over DTCA since the staffing has not kept pace with the proliferation of DTCA,[xi] nor has Congress provided sufficient funding to support quality, independent research on the impact of DTCA. These concerns are discussed in more detail later in this testimony.

AMA Policy and DTCA

In June 2006, in light of the rapid proliferation of DTCA, climbing health care costs, and concerns about the negative impact of DTCA on patient-physician relations, the AMA adopted a comprehensive set of recommendations, in addition to guidelines for an appropriate DTC ad, to ensure that DTCA is properly regulated and assessed to ensure it does not adversely impact patient-physician relations, provides appropriate and balanced information, and does not artificially increase health care costs by causing overutilization.

In general, the AMA supports "help-seeking" or "disease awareness" ads (i.e., ads that discuss a disease, disorder, or condition and advise consumers to see their physicians, but do not mention a drug or implantable medical device or other medical product and are not regulated by the FDA). The AMA opposes "product-specific" DTCA, regardless of medium, that is not consistent with the following guidelines.

- Indication-Specific and Educational. The ad should be indication-specific and enhance consumer education about both the drug or implantable medical device, and the disease, disorder, or condition for which the drug or device is used.

- Accurate and Objective Information on Risk as well as Benefit. In addition to creating awareness about a drug or implantable medical device for the treatment or prevention of a disease, disorder, or condition, the ad should convey a clear, accurate, and responsible health education message by providing objective information about the benefits and risks of the drug or implantable medical device for a given indication. Information about benefits should reflect the true efficacy of the drug or implantable medical device as determined by clinical trials that resulted in the drug's or device's approval for marketing. Risk information should be clearly stated and comprehensible to the consumer.

- Prescription Required. The ad should clearly indicate that the product is a prescription drug or implantable medical device to distinguish such advertising from other advertising for non-prescription products.

- Encourage Physician Consultation. The ad should not encourage self-diagnosis and self-treatment, but should refer patients to their physicians for more information. A statement, such as "Your physician may recommend other appropriate treatments," is recommended.

- Fair Balance Between Risk and Benefit Information. The ad should exhibit fair balance between benefit and risk information when discussing the use of the drug or implantable medical device product for the disease, disorder, or condition. The amount of time or space devoted to benefit and risk information, as well ease with which people can find, understand, remember, and use the information, should be comparable.

- Clear Communication of Warnings, Precautions, and Potential Adverse Reactions. The ad should present information about warnings, precautions, and potential adverse reactions associated with the drug or implantable medical device product in a manner (e.g., at a reading grade level) such that it will be understood by a majority of consumers, without content and devices designed to minimize or distract from risks, and will help facilitate communication between physician and patient.

- No Actors Playing Doctor Unless Clear Disclaimer Provided. In general, ads should not use an actor to portray a health care professional who promotes the drug or implantable medical device product because this portrayal may be misleading and

deceptive. If actors portray health care professionals in DTCA, a disclaimer should be prominently displayed.

- No Actual Health Care Professionals Unless Clear Disclaimer Provided. The use of actual health care professionals, either practicing or retired, in DTCA to endorse a specific drug or implantable medical device product is discouraged, but if utilized, the ad must include a clearly visible disclaimer that the health care professional is compensated for the endorsement.

- Age Appropriate Placement. The ad should be targeted for placement in print, broadcast, or other electronic media so as to avoid audiences that are not age appropriate for the messages involved.

- Comply with FDA Regulations. The ad must comply with all other applicable FDA regulations, policies, and guidelines.

In addition, the AMA's policy includes support for enhanced FDA authority to regulate DTCA. Specifically, the AMA has advocated for FDA authority to review—and pre-approve—all DTC ads for prescription drug or implantable medical device products before pharmaceutical and medical device manufacturers run the ad.

The AMA has called upon the FDA to require that all newly approved prescription drug or implantable medical device products should be subject to a DTCA moratorium until

physicians have been appropriately educated about the drug or implantable medical device. Our policy provides that the time interval for this moratorium on DTCA should be determined by the FDA, in negotiations with the drug or medical device product's manufacturer, at the time of drug or implantable medical device approval. The length of the moratorium may vary from drug to drug and device to device depending on various factors, such as:

- the innovative nature of the drug or implantable medical device;
- the severity of the disease that the drug or implantable medical device is intended to treat;
- the availability of alternative therapies; and,
- the intensity and timeliness of the education about the drug or implantable medical device for physicians who are most likely to prescribe it.

The AMA encourages the FDA, other appropriate federal agencies, and the pharmaceutical and medical device industries to conduct or fund research on the effect of DTCA, focusing on its impact on the patient-physician relationship as well as overall health outcomes and cost benefit analyses.

To that end, the AMA also supports actions by Congress to require that the Agency for Healthcare Research and Quality (AHRQ) perform periodic evidence-based reviews of DTCA in the United States to determine the impact of DTCA on health outcomes and the public health. If DTCA is found to have a negative impact on health outcomes and is

detrimental to the public health, then Congress should consider enacting legislation to increase DTCA regulation or, if necessary, prohibit DTCA in some or all media. (Incidentally, the Institute of Medicine has already recommended that the FDA restrict advertising for newer prescription drugs in a study of drug safety.)[xii] In such legislation, every effort should be made not to violate protections on commercial speech, as provided by the First Amendment to the U.S. Constitution.

AMA's current policy recognizes that DTCA is legal and widespread. While the AMA's guidelines for acceptable DTCA have generally been well received by both the FDA and the Pharmaceutical Research and Manufacturers of America (PhRMA), regrettably the member companies of PhRMA have not consistently complied with the AMA's guidelines.

Key AMA Concerns about DTCA

Significant ongoing concerns and questions about DTCA within the physician community, include: 1) does DTCA provide educational value, are ads fairly balanced, and do they adequately disclose risks to consumers; 2) what is the impact of such ads on patient-physician relationships; and 3) what is the impact of such ads on health care utilization and costs? Each of these concerns/questions is addressed below.

1. Is DTCA Educational and Balanced?

The bedrock of AMA's guidelines is that DTCA should be educational, and not misleading. Do most product-specific ads meet the AMA's standard for educational

value? This is difficult to answer, since what is educational to one individual may not be to another. While good data is hard to find on this issue, the majority of physicians most likely would not agree that the ads are educational. In one study that was published in the December 2000 issue of the *Journal of Family Practice*, the researchers reviewed over 300 print ads for 101 prescription drug products in 18 popular magazines over the previous decade. They found that while the ads were informative, they lacked important educational information about the condition and the treatment for which the drug was being promoted.[xiii]

Similarly, researchers in another study reviewed the contents of 67 DTC ads from 10 magazines published between July 1998 and July 1999. They found that the ads rarely quantified a medication's expected benefit, and instead made an emotional appeal.[xiv] In contrast, more than one-half of the ads used data to describe a drug's side effects.[xv] The authors suggested that these DTC ads leave readers with the perception that the drug's benefit is large and that everyone who uses the drug will enjoy the benefit.[xvi]

In yet another study, concerns were raised about the educational value of television DTC ads.[xvii] These investigators reviewed 23 television DTC ads and found the ads provided insufficient information about risks, and that the ads lacked fair balance between benefit and risk information.[xviii] They also found that the ads often used medical terminology that was not consumer-friendly, especially for patients with limited literacy.[xix] More recently, researchers reviewed 31 product-specific DTC TV ads and concluded the ads lacked educational value.[xx] These TV ads provided limited information about the causes

of a disease or who may be at risk, they show characters that have lost control over their social, emotional, or physical lives without the medication, and they minimize the value of health promotion through lifestyle changes.[xxviii]

Although increased access by patients to accurate, objective information about tests to diagnose and drugs to treat illnesses is certainly important, there is the risk of confusion when commercially-driven promotional information is presented as educational. The issue is not whether consumers should obtain more information about treatment options; the real question is whether DTCA, with its aim of selling a product, can provide the type of information consumers need or should have. Advertising has been described by one economist as "the science of arresting the human intelligence long enough to get money from it."[xxi] One executive of an advertising agency that focuses on DTCA has noted that "consumers react emotionally, so you want to know how they feel about your message and what emotional triggers will get them to act.... We want to identify the emotions that we can tap into to get that customer to take the desired course of action."[xxii]

In addition to assessing the educational value of DTCA, the AMA is concerned that consumers are not consistently receiving a balanced view of the benefits and risks of a product based on advertising. The FDA has made efforts to guide manufacturers to provide consumers with risk information, based on the drug's labeling, that is more useful and easily understood. For the most part, the AMA would concur that fair balance and adequate disclosure of risks appear in print ads, which require the "brief summary" (which usually is identical text to the risk sections [i.e., warnings, precautions and side

effects] in FDA-approved professional labeling [Package Insert, PI] to be included. Unfortunately, the "brief summary" has long been criticized by many stakeholders as too difficult for consumers to understand. The AMA has submitted comments to the FDA supporting the presentation of risk information in a more consumer-friendly way, so that key risks about prescription drug products will be better understood.

For television ads, however, studies indicate that DTCA in this medium has not provided fair balance between benefit and risk information. In one study, after viewing DTC TV ads, people were about 80 percent correct in identifying the benefits of the advertised drug, but only 20 percent correct in describing the side effects.[xxiii] In the same study, the researchers found that about three times more sentences were devoted to benefit information when compared to risk information, and that the placement of risk information was such that consumers would be least likely to remember it. Also, an individual would need only about a 6th grade reading level to understand the benefits of the advertised drug, but a 9th grade level for side effects. The authors concluded that the cognitive accessibility, defined as the ease with which people can find, understand, remember, and use information, was far better for benefit information when compared to risk information in DTC TV ads.

In yet another study, researchers found that the mean television DTC ad length was 46.3 seconds, but only 6.3 seconds on average discussed side effects. Also, the vast majority of the ads (90 percent) placed risk information in the middle or the end of the ad where it would be less likely to be remembered.[xxiv] Some of the ads also were very effective at

using pleasing, not to mention distracting, visuals as the major risk information was being discussed in audio only.

Finally, some studies have shown that patients have potentially dangerous misperceptions about DTCA. One research study suggested that one-half of consumers incorrectly believed that DTC ads are pre-approved by the FDA, and 43 percent incorrectly believed that only completely safe drugs can be advertised directly.[xxv] Another study found that consumers rated the safety and appeal of drugs described with an incomplete statement of risks more positively than similar drugs described with a more complete statement of risks.[xxvi] These perceptions raise the question of whether widespread DTCA is giving consumers a false sense of security that prescription drugs are risk-free.

2. What is the Impact of DTCA on the Patient-physician Relationship?

The AMA remains concerned about the impact of DTCA on the patient-physician relationship and the paucity of quality, independent peer-reviewed research to measure this impact. The consumer surveys that have been conducted, such as those by the FDA, *Time*, the AARP, the National Consumers League and *Prevention* magazine, suggest that DTCA increases: (1) physician office visits; (2) new diagnoses; (3) informed discussion between physician and patient about conditions and treatments; and, (4) unfortunately in some cases, demand for a specific advertised drug product. In a 2002 report by the Government Accountability Office (GAO), the authors examined a number of consumer surveys and concluded that the percentage of consumers who, in response to a DTCA, requested and received a prescription from their physician for a drug they were not

currently taking was generally about 5 percent. The GAO estimated that this meant that about 8.5 million consumers in 2000 received a prescription drug after viewing a DTC ad and asking their physician for the drug.[xxvii]

Although DTCA might have the positive effect of increasing physician office visits, resulting in the diagnosis of previously undiagnosed conditions, and in better communication between physician and patient, many physicians complain that patients, armed with the latest DTC ad, come into their offices demanding the physician prescribe the advertised drug for them. If a medication is not necessary or appropriate, the physician is put in the uncomfortable and awkward position of defending why this is the case. Less time is available to diagnose and treat the patient if the patient has a fixation on a particular drug as a result of a commercial. This can add strain and potentially distrust to a relationship that should be completely open.

A FDA survey of physicians, strongly supported by the AMA, released in January 2003 concluded that most physicians view DTCA as one of many factors that affect their practice and their interactions with patients, both positively and in some respects, negatively. The FDA survey also found that physicians felt they had to provide additional information to patients beyond what patients retained from the DTCA. About 75 percent of physicians believed that DTCA causes patients to think the drug works better than it did, and many physicians felt some pressure to prescribe something when patients mentioned an ad. The FDA survey also found that about eight percent of physicians felt very pressured to prescribe the specific brand name drug when asked

about it.[xxviii] Various surveys and limited research studies have shown that some physicians prescribe the requested drug. One would like to believe that objective treatment decisions were made in every case. However, the question needs to be raised as to whether clinical judgment is being compromised in some cases to preserve a positive relationship with the patient.

3. What is the Impact of DTCA on Health Care Costs and Utilization?

The AMA also is concerned about the impact of DTCA on health care costs and utilization. DTCA is targeted at an audience that often is not responsible for paying for the product because most prescriptions are paid for, at least in part, by private or public insurance. The key question is whether these increased costs for advertised drugs are reducing costs in other health care areas so that the net effect is more cost-effective health care. This also places the physician in a difficult situation. On the one hand, the payer expects the physician to be cost-conscious and not prescribe the most expensive drug, if not medically indicated. On the other hand, payers also grade physicians based on patient satisfaction. The physician faces pressure from the patient requesting an expensive advertised drug and pressure from the payer to prescribe comparable but less expensive alternatives.

Limited studies have concluded that DTCA does, in fact, lead to increased spending on drugs. A study by researchers at the Harvard School of Public Health, Massachusetts Institute of Technology, and Harvard Medical School for the Kaiser Family Foundation, released in June 2003, found that increases in DTCA have a significant impact on drug

spending growth. The authors estimated that in 2000, 12 percent of drug spending growth was related to increased spending on DTCA.[xxix] Each additional dollar spent on DTCA yielding an additional $4.20 in drug sales in that year.[xxx]

In 2002, the GAO also found that drugs promoted directly to consumers often were among the best-selling drugs, and sales for DTC-advertised drugs increased faster than sales for drugs that are not heavily advertised to consumers. Moreover, the GAO found that most of the spending increase for heavily advertised drugs was the result of increased utilization rather than price increases.[xxxi] A more recent GAO report in November 2006 also concluded that DTCA appeared to increase prescription drug spending and utilization.[xxxii]

A recent Kaiser Foundation, USA Today, and Harvard School of Public Health consumer survey found that about one-third of consumers have talked to a physician about a prescription drug they saw advertised.[xxxiii] Among this group, 44 percent said their physician prescribed them a drug they asked about, and 54 percent say their physician recommended another prescription drug (resulting in 82 percent who received a prescription either for the drug they asked about and/or another drug).

These studies may reflect an appropriate increase in spending on drug treatments that were previously underutilized. Alternatively, this also could reflect wasteful spending on expensive advertised drugs for which less expensive alternatives, or no drug at all, will work just as well. A clear answer to this important question is definitely needed.

Recommendations

The AMA offers the following conclusions and recommendations to the Subcommittee as it examines the consequences of DTCA:

1. The AMA believes there is substantial room for improvement in the educational value of DTCA. In this regard, the AMA urges the pharmaceutical and medical device industries to use and comply with the AMA's guidelines for DTCA. Responsible DTCA that is accurate and educational to consumers, that balances benefits and risks, and that promotes good health outcomes could have a positive impact on health care.

2. The AMA believes that consumers must be better educated to understand the limitations of DTCA. The AMA stands ready to work with the FDA and consumer groups in such an educational endeavor.

3. The AMA supports more independent research on DTCA and, particularly, on its impact on the patient-physician relationship and on health outcomes and costs. In light of recent events involving aggressively marketed new drugs with significant safety risks, the need to examine the impact of DTCA on patient safety also has become a priority. The results of this research must be published in reputable, peer-reviewed journals and be available in the public domain. The AMA believes

that both industry and government have an obligation to fund this research. Such research should guide future regulation of DTCA.

4. The FDA should pre-review and approve all DTC ads, and should determine the length of any moratoriums on DTC ads for new drugs and medical devices.

5. For its part, the AMA will continue to educate physicians on their role in identifying and reporting inappropriate DTC ads, in cooperating with research studies to better understand and evaluate the impact of DTCA, and to assure they are meeting their ethical duties to their patients in recommending appropriate treatments.

The AMA is pleased to have the opportunity to share with the Subcommittee the AMA's policy on DTCA and information on the impact it has on the patient-physician relationship, the quality of the information it provides to patients, and the role it may play in escalating health care costs. We look forward to working with the Subcommittee to promote and protect the interests of patients and consumers by ensuring that DTCA is accurate, balanced, and enhances the patient-physician relationship while not causing over utilization or promotion of expensive new drugs with limited safety profiles.

Endnotes

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Mr. STUPAK. Thank you, Doctor. And Dr. Brodie, for your opening statement. If you would, push that button right there on that mic, and you might have to pull that up a little bit.

STATEMENT OF MOLLYANN BRODIE, PH.D., VICE PRESIDENT AND DIRECTOR, PUBLIC OPINION AND MEDIA RESEARCH, KAISER FAMILY FOUNDATION

Ms. BRODIE. Mr. Chairman, and member of the Oversight and Investigations Subcommittee, thank you for the opportunity to testify today on the public's views of direct-to-consumer prescription drug advertising. I am Mollyann Brodie, vice president and director of public opinion and medical research at the Kaiser Family Foundation. Despite the fact that they account for just 10 percent of healthcare spending over all prescription drugs and their costs have become a central healthcare affordability and access issue in the views of the American public, mainly because they touch almost everyone. More than half of Americans regularly take perception drugs, and four in ten report some serious problem paying for their medications, including having to skip doses because of the cost.

The public has mixed views of prescription drugs and the companies that make them. On the positive side, they appreciate the benefits for the drugs themselves and most people agree that medications have had a positive impact on their own lives and the lives of Americans in general. However, on the negative side, they are very concerned about high drug prices, which nearly eight in ten say are unreasonable, and which, in the public's views are largely driven by high company profits. Prescription drug advertisements have become ubiquitous, and nine in ten adults report having seen or heard advertisements for medications. Americans have mixed views about the relative benefits and costs associated with these ads. On the one hand, most Americans agree with the proponents of the drug ads, who say that they raise awareness, help educate the public, and reduce stigma. On the other hand, most people agree with the critics of the ads, who say they raise prescription drug prices and induce unnecessary demand.

Further, the public's views are mixed about how well the drug ads present specific information about the medicines they advertise. While the majority say they do a good job explaining the potential benefits and what condition the drug is designed to treat, more than half say they do only a fair or poor job explaining the potential side effects. The survey data strongly suggests that the drug advertisements are doing what they were designed to do: prompting people to talk to their doctors and to get prescriptions. About a third of Americans report that they have talked to a doctor about a specific drug after seeing an ad, and about eight in ten of that group said that the doctor recommended a prescription as a result, either for the drug they asked about or for another medication. People report that these discussions led to other actions as well. For example, more than half of those who talked to their doctor about a specific drug say the physician recommended lifestyle or behavioral changes, while about three in ten said the doctor recommended an over-the-counter drug.

Now, these findings are echoed in surveys we have done with physicians who are involved in direct patient care, a large majority of whom report both getting inquires from patients based on drug ads, and at least sometimes recommending a prescription drug as a result. Eight in ten physicians say that patients asked them about specific diseases or treatments that they had heard about from ads, at least sometimes, including nearly three in ten who say they frequently get such inquiries. When asked what actions they usually take when the patients ask them about mediations, the most common response is recommending a lifestyle or behavioral change, which half of doctors say they do so frequently. Doctors are less likely to day they frequently give a prescription for the requested drug. However, about three-quarters say they at sometimes recommend a different medication, and more than half said that they at least sometimes give the patient a prescription for the drug they asked about.

What the survey data can't tell us is whether this advertising induced demand is good or bad from a health perceptive. It is mostly encouraging people who might not otherwise get treatment to seek needed medication, or is it mostly leading to demand for unnecessary medications? These are questions that go beyond the scope of what the public can tell us in a survey. Given that ultimately the doctor must decide whether or not to write the prescription, it is helpful to recognize that the majority of the physicians do not seem to think that these inquiries from patients are negatively impacting their doctor-patient relationship, although about one in five say that they do.

The data also shows that the public prioritizes affordability of prescription drugs, and while government regulation in many areas is unpopular, there is an appetite among many for increased government regulation when it comes to reining in prescription drug prices. Furthermore, typical arguments against such actions do not substantially erode this public support. To a lesser degree, some, about four in ten, are supportive of more regulation in terms of making sure advertising claims are not misleading, although many believe that there is already enough regulation in this area. However, since the public has both become more skeptical of drug ads over time, and gives these ads low scores on their ability to effectively communicate about potential side effects, the public would likely welcome efforts that may lead to improvements in prescription drug advertising practices.

Thank you for the opportunity to testify today and for your attention to the public's views on this important matter. I welcome your questions.

[The prepared statement of Ms. Brodie follows:]



Public Views of Direct-to-Consumer Prescription Drug Advertising

Mollyann Brodie, Ph.D.
Vice President and Director, Public Opinion and Media Research,
Henry J. Kaiser Family Foundation

Testimony before the
U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

May 8, 2008

SUMMARY OF TESTIMONY BY MOLLYANN BRODIE, PH.D.

- Despite the fact that they account for just 10 percent of health care spending overall, prescription drugs and their cost have become a central health care affordability and access issue, mainly because they touch almost everyone's lives in some way. More than half of Americans regularly take prescription drugs, and four in ten report some serious problem paying for their medications.

- The public has mixed views of prescription drugs and the companies that make them. On the positive side, they appreciate the benefits of the drugs themselves, while on the negative side, they are concerned about high drug prices, which in their view are largely driven by high company profits.

- The public also sees both a good and a bad side to prescription drug advertising. On the one hand, most Americans agree with the proponents of drug ads who say that they raise awareness, help educate the public, and reduce stigma. On the other hand, most people agree with critics of these ads who say they raise prescription drug prices and induce unnecessary demand.

- Further, the public's views are mixed about how well drug ads present specific information about the medicines they advertise. While majorities say they do a good job explaining the potential benefits and what condition the drug is designed to treat, more than half say ads do only a fair or poor job explaining potential side effects.

- Survey data strongly suggest that drug advertisements are doing what they were designed to do – prompting people to talk to their doctors and to get prescriptions. About a third of Americans report that they have talked to a doctor about a specific drug after seeing an ad, and about eight in ten of this group says the doctor recommended a prescription drug as a result. These findings are echoed in surveys of physicians, a large majority of whom report both getting inquiries from patients based on drug ads and at least sometimes recommending a prescription drug as a result of these inquiries.

- What the survey data can't tell us is whether this "advertising induced demand" is good or bad from a health perspective – is it mostly encouraging people who might not otherwise get treatment to seek needed medications, or is it mostly leading to demand for unnecessary medications? These questions go beyond what the public can tell us in a survey.

- Finally, while government regulation in many areas is unpopular, there is an appetite among some in the public for increased government regulation when it comes to prescription drugs in terms of both making sure advertising claims are not misleading and in helping to rein in prices, and typical arguments against such regulation do not substantially erode public support.

Introduction

Mr. Chairman and members of the Oversight and Investigations Subcommittee, thank you for the opportunity to testify today on the public's views of direct-to-consumer prescription drug advertising. I am Mollyann Brodie, Vice President and Director of Public Opinion and Media Research of the Henry J. Kaiser Family Foundation. The Kaiser Family Foundation is a non-profit, private operating foundation dedicated to providing information and analysis on health care issues to policymakers, the media, the health care community and the general public. The Foundation is not associated with Kaiser Permanente or Kaiser Industries. My testimony today will briefly review what we know from public opinion surveys about Americans' opinions of and experiences with prescription drugs and pharmaceutical companies in general, with a more specific focus on their views of direct-to-consumer advertising. The data I will share with you today are based on nationally representative surveys of the general public that Kaiser Family Foundation researchers have conducted on these topics over the past several years, the most recent of which was conducted in January 2008[1]. I will also share some data from a 2006 Kaiser survey of physicians involved in direct patient care[2].

Despite the fact that they account for just 10 percent of health care spending overall[3], prescription drugs and their cost have become a central health care affordability and access issue, mainly because they touch almost everyone's lives in some way. Prescription drugs play a role in the daily lives of more than half of all Americans, and most people agree that these

[1] Unless otherwise noted, survey data presented in this testimony are from the USA Today/Kaiser Family Foundation/Harvard School of Public Health survey, *The Public On Prescription Drugs and Pharmaceutical Companies*, a nationally representative random sample survey of 1,695 adults ages 18 and older, conducted by telephone in English and Spanish from Jan. 3-23, 2008. The margin of sampling error for the survey is plus or minus 3 percentage points.

[2] Physician survey data presented in this testimony are from the Kaiser Family Foundation *National Survey of Physicians*, a nationally representative random sample survey of 834 office-based physicians involved in direct patient care with adults, conducted by telephone and online from April 25-July 8, 2006. The margin of sampling error for the survey is plus or minus 3 percentage points.

[3] Source: Kaiser Family Foundation calculations using National Health Expenditure data from Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group. Available at: http://www.kff.org/insurance/upload/7670.pdf.

medications have had a positive impact on their own lives and on the lives of Americans in general. While they appreciate the products that pharmaceutical companies produce, the public holds less favorable views towards the companies themselves; 47 percent say they have a favorable view of pharmaceutical companies, while nearly as many – 44 percent – have an unfavorable view. Among the seven types of organizations asked about, only health insurance companies (54 percent) and oil companies (63 percent) are viewed unfavorably by more Americans (Figure 1).

The main reason behind these unfavorable views is the public's concern about high drug prices, which in their view are largely driven by high company profits; nearly eight in ten Americans say the cost of prescription drugs is unreasonable, seven in ten say that pharmaceutical companies are too concerned about making profits and not concerned enough about helping people, and eight in ten say that profits made by drug companies are a major contributing factor in the price of prescription drugs (Figure 2).

These opinions about prices and profits may be related, at least in part, to people's real-life struggles paying for drugs. Four in ten adults report some serious problem paying for medication, including 29 percent who say they have not filled a prescription because of the cost in the past two years, 23 percent who report skipping doses or cutting pills in half to make their prescription last longer, and 16 percent who say it is a serious problem for their family to afford the drugs they need (Figure 3). Problems paying for prescription drugs, not filling prescriptions because of cost, and skipping doses are even more common among those who take four or more prescription drugs (59 percent), those who don't have insurance to cover their prescription drug costs (52 percent), and those with lower incomes (54 percent of those earning less than $25,000).

Views of Prescription Drug Advertising

Prescription drug advertisements have become ubiquitous in the media, and in 2008, 91 percent of adults report having seen or heard advertisements for prescription drugs (up from 76 percent in 2000[4]). While nearly all Americans have seen or heard prescription drug ads, they have mixed views about the relative benefits and costs associated with them. On the one hand, when it comes to general opinions about these ads, more people view them as mainly positive than as negative. Just over half (53 percent) of the public says prescription drug advertising is mostly a good thing, while 40 percent say it is mostly a bad thing. Two-thirds of the public agrees that prescription drug advertisements educate people about available treatments and encourage them to get help for medical conditions they might not have been aware of (Figure 4).

More people also see benefits from advertisements for prescription drugs that treat mental health conditions like depression and anxiety. Six in ten think such ads are mostly good because they improve understanding of these conditions and encourage people to seek treatment, while just over a third (36 percent) think these ads are mostly bad because they encourage people without serious mental health conditions to think they need treatment (Figure 5).

On the other hand, the public has concerns about drug advertisements, and views are mixed about how well these ads present specific information about the medicines they advertise. While majorities say drug ads do an "excellent" or "good" job explaining the potential benefits of a medication (56 percent) and what condition it is designed to treat (54 percent), more than half (53 percent) say ads do only a "fair" or "poor" job explaining the potential side effects of the medication (Figure 6). In addition, advertisements rank at the bottom of the list of sources people rely on for information about prescription medications. Just over a quarter (27 percent) of

[4] Source: Kaiser Family Foundation/Agency for Health Care Research and Quality, *National Survey on Americans as Health Care Consumers,* a nationally representative random sample survey of 2,014 adults ages 18 and older, conducted by telephone from July 31-Oct. 9, 2000, margin of sampling error plus or minus 3 percentage points.

adults say they rely on drug advertisements "a lot" or "somewhat" to provide accurate information about prescription drugs, ranking lowest on the list of seven sources asked about (Figure 7). Ranking highest on the list of sources people rely on for information about drugs are doctors (91 percent), pharmacists (81 percent), and information about the product included in the manufacturer's packaging (81 percent).

The public has become more skeptical of drug ads over time as trust in pharmaceutical company advertising has declined. In 1997[5], a third of adults said they could trust what drug companies had to say in their advertisements "most of the time"; by 2005[6] this share had declined to 18 percent (Figure 8). Perhaps as a result of this declining trust, there is an appetite among some in the public for increased government regulation of prescription drug advertising; while a plurality (48 percent) say there is about the right amount of regulation aimed at making sure these ads are not misleading and six percent say there is too much, more than four in ten (43 percent) say there should be more regulation in this area (Figure 9). More of the public favors regulation when it comes to drug prices; two-thirds say there should be more regulation limiting the price of prescription drugs, and even when the argument that this might lead companies to do less R&D is mentioned, nearly half support price regulation.

The public is also concerned about the cost of prescription drug ads and the impact of these costs on drug prices overall, as well as about increased consumer demand for drugs caused by advertising. Six in ten say pharmaceutical companies spend too much money advertising to patients, and roughly half (51 percent) say they spend too much on marketing to doctors (Figure 10). About three in four (77 percent) believe that the cost of advertisements makes prescription

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[5] Source: Kaiser Family Foundation/Harvard School of Public Health, *Views on Managed Care Survey*, a nationally representative random sample survey of 1,204 adults ages 18 and older conducted by telephone Aug. 22-Sept. 23, 1997; margin of sampling error plus or minus 3 percentage points.

[6] Source: Kaiser Family Foundation, *Health Poll Report Survey*, a nationally representative random sample survey of 1,201 adults ages 18 and older conducted by telephone February 3-6, 2005; margin of sampling error plus or minus 3 percentage points.

drugs too expensive, and four in ten (41 percent) say this bothers them "a lot." Among other concerns, about two-thirds believe there are too many prescription drug ads on television (68 percent) and that ads encourage people to take medications they don't need (66 percent); however, fewer say they are bothered "a lot" by either of these issues (27 percent and 34 percent, respectively) (Figure 11).

Talking to Doctors as a Result of Drug Ads

Our survey suggests that the drug advertisements are prompting people to talk to doctors and to get more prescription drugs. Nearly one-third (32 percent) of adults say they have talked to a doctor about a specific prescription medication they saw in an advertisement, and more than eight in ten of those who talked to a doctor about a drug they saw advertised (representing 26 percent of all adults) say the doctor recommended a prescription, either for the drug they asked about or another prescription drug. More than half (57 percent) of those who talked to a doctor after seeing an ad say their doctor recommended lifestyle or behavior changes, while three in ten say the doctor recommended an over-the-counter drug (Figure 12).

Physicians' Views

Like the public, physicians are somewhat split when it comes to the usefulness of prescription drug ads. In a 2006 survey of office-based physicians involved in direct patient care with adults, just over half (53 percent) of doctors said that drug company advertisements provide useful information for patients "most of the time" or "sometimes," while nearly as many (47 percent) said these ads "hardly ever" or "never" provide useful information for patients.

Eight in ten physicians (80 percent) say that patients ask them about specific diseases or treatments they heard about from advertisements for prescription drugs at least "sometimes," including nearly three in ten (28 percent) who say they "frequently" get such inquiries from patients. Large shares of physicians also say that patients frequently or sometimes ask them

about diseases or treatments they heard about from friends or family members (89 percent), the general news media (84 percent), and the Internet (71 percent), while fewer say patients ask them about treatments they heard about from entertainment TV shows (36 percent) (Figure 13).

A plurality (42 percent) of physicians say that when patients ask them about specific diseases or treatments they heard about from prescription drug ads or other sources, these inquiries have a positive impact on their interactions with patients. About a third (35 percent) say these inquiries have no effect on their interactions with patients, while about one in five (21 percent) say they have a negative impact (Figure 14).

When asked what actions they usually take when patients ask them about treatments they heard about from prescription drug ads or other sources, the most common response given by doctors is recommending lifestyle or behavior changes; half of doctors say they do this "frequently" when they get such inquiries from patients, and another 42 percent say they do this "sometimes." Doctors are less likely to say they frequently recommend an over-the counter drug (18 percent), recommend a different prescription drug (14 percent), recommend no treatment (14 percent), or give the patient a prescription for the drug they asked about (5 percent). However, a majority of doctors say they at least sometimes recommend a different prescription drug (76 percent) or give the patient a prescription for the drug they asked about (57 percent) (Figure 15).

Conclusions

The public has mixed views of pharmaceutical companies and the advertising they produce. On the one hand, most Americans agree with the proponents of drug ads who say that they raise awareness, help educate the public, and reduce stigma. On the other hand, most people agree with critics of these ads who say they raise prescription drug prices and lead some people to take medications they don't really need.

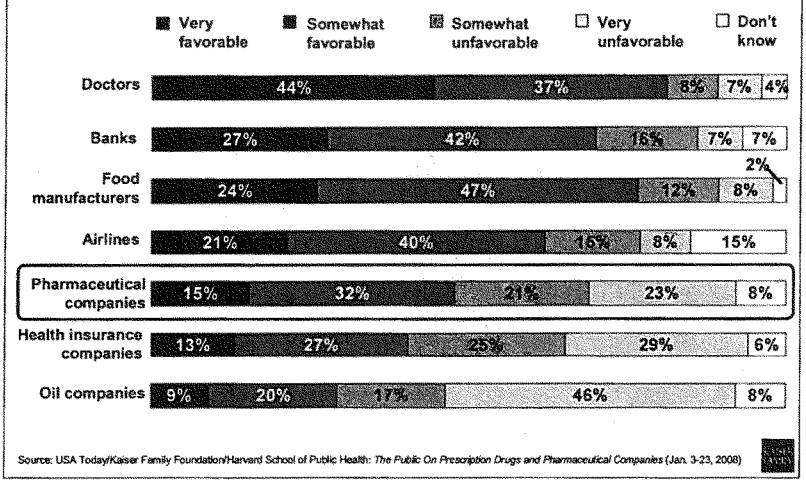
We know from our survey data that prescription drug ads are doing what they are designed to do – prompting people to talk to their doctor about a specific drug they saw advertised. Many go on to receive a doctor's recommendation for a prescription as a result. What we don't know is what share of those people were already under a doctor's care for that particular condition and were asking about a new drug, how many were prompted by an ad to get needed care for a condition they hadn't discussed with a doctor before, or how many may have been seeking unnecessary medications. These questions go beyond the scope of what can be captured in a survey of the public. Given that, ultimately, the doctor must decide whether or not to write the prescription, it is helpful to recognize that the majority of doctors do not seem to think these inquiries from patients are negatively impacting their doctor-patient relationship.

The public prioritizes affordability of prescription drugs, and while government regulation in many areas is unpopular, there is an appetite among many for increased government regulation when it comes to reining in prescription drug prices. To a lesser degree, some are supportive of more regulation in terms of making sure advertising claims are not misleading, although many believe there is already enough regulation in this area. However, since the public has both become more skeptical of drug ads over time and gives these ads low scores on their ability to effectively communicate about potential side effects, the public would likely embrace efforts that may lead to improvements in prescription drug advertising practices.

Thank you for the opportunity to testify today and for your attention to the public's views on this matter. I welcome your questions.

Figure 1

General Opinions of Pharmaceutical Companies and Other Groups

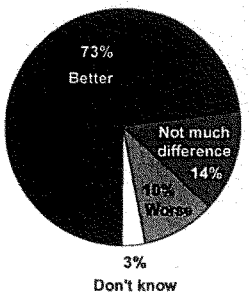


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2008)

Figure 2

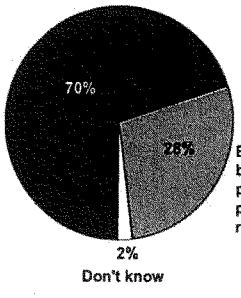
Positive and Negative Views of Drug Companies

Do you think prescription drugs developed over the past 20 years have generally made the lives of people in the US better, worse or haven't they made much difference?



Which statement comes closer to your view?

Drug companies are too concerned about profits, not concerned enough about helping people

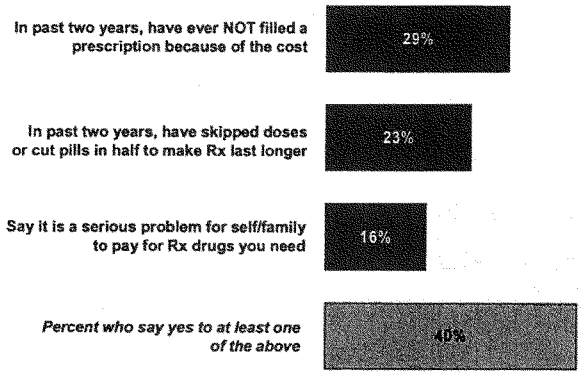


Balance of concern between making profits and helping people is about right

Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2008)

Figure 3

Four in Ten Report At Least One Serious Problem Affording Prescription Drugs

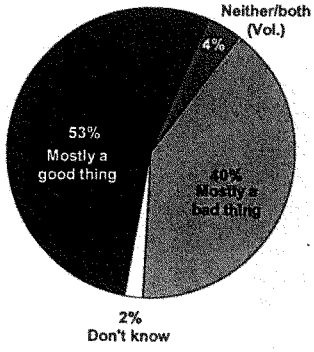


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2008)

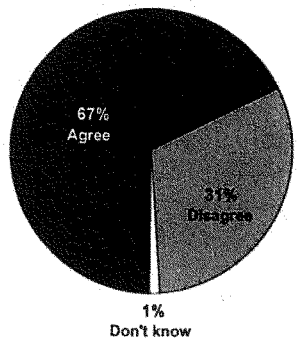
Figure 4

More View Rx Drug Ads As Positive than Negative

On balance, do you think prescription drug advertising is mostly a good thing, or mostly a bad thing?



Do you agree or disagree with this statement: Prescription drug ads educate people about available treatments and encourage them to get help for medical conditions they might not have been aware of

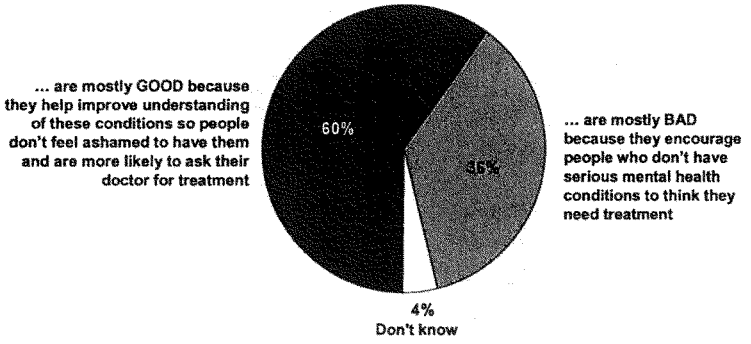


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2008)

Figure 5

Perception of Drug Ads for Mental Health Conditions

Which comes closer to your view:
Advertisements for prescription drugs to treat mental health conditions like depression and anxiety...?

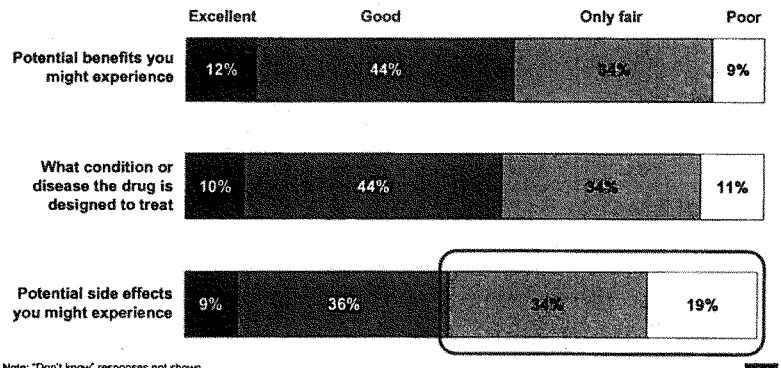


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2006)

Figure 6

Most Think Drug Ads Do a Decent Job Informing the Public (except when it comes to side effects)

Do prescription drug advertisements do an excellent job, a good job, only a fair job, or a poor job telling you about the following... ?



Note: "Don't know" responses not shown
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2006)

Figure 7

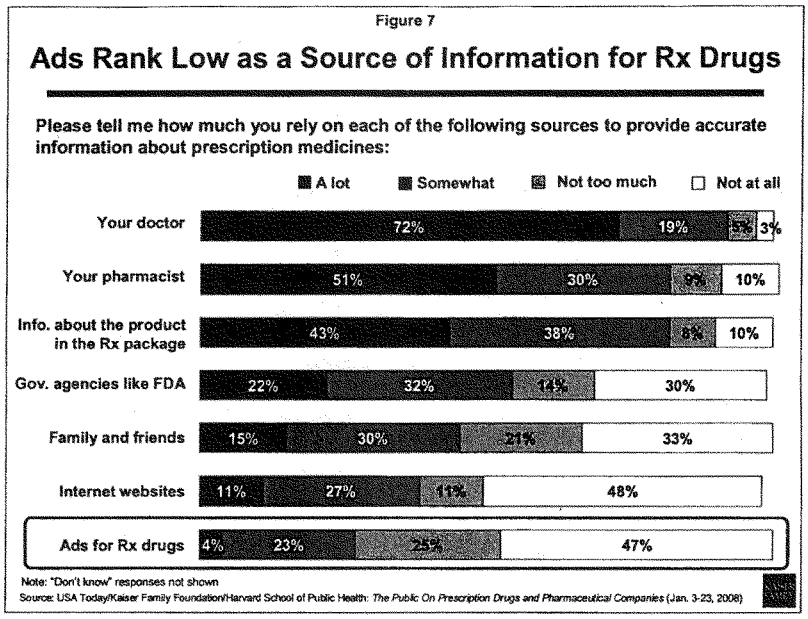


Figure 8

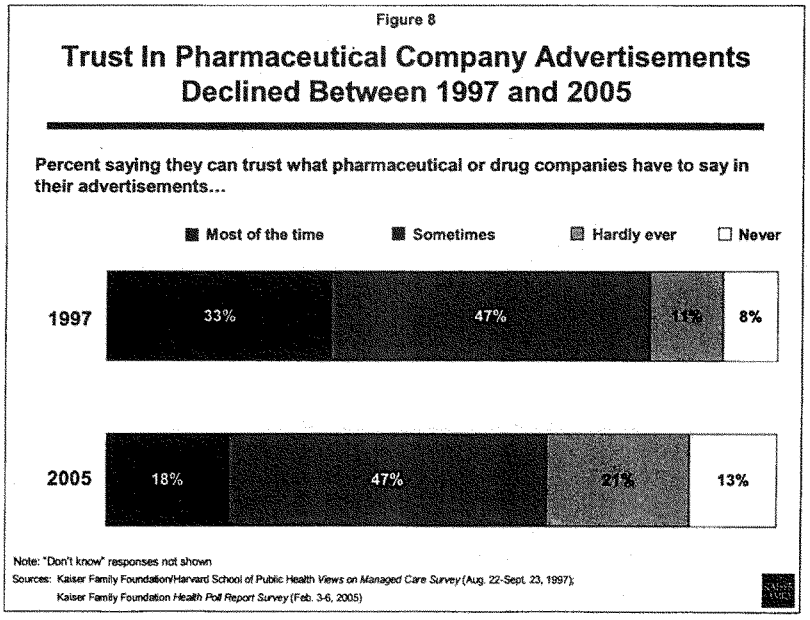
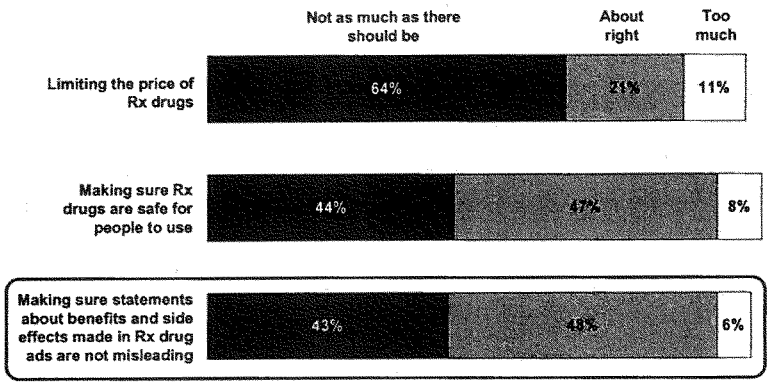


Figure 9

Most Think There is Enough Government Regulation of Rx Drug Ads, Though Many Would Like to See More

Percent saying the amount of government regulation in each area is...



Note: "Don't know" responses not shown

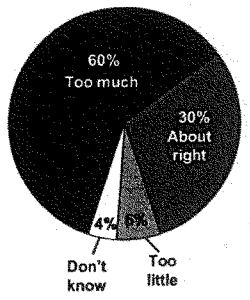
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2008)

Figure 10

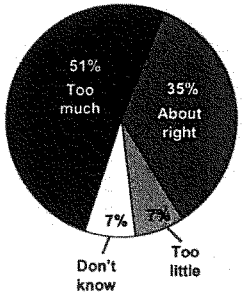
Perception of Pharmaceutical Companies' Spending on Advertising and Marketing

Do you think pharmaceutical companies spending too much, too little, or about the right amount of money on...

...Advertising to patients



...Marketing their products to doctors



Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2008)

Figure 11

Some Negative Views of Rx Drug Ads

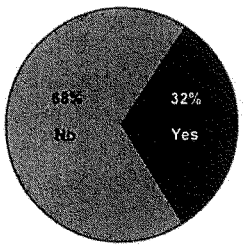
Negatives of prescription drug ads	% who agree with each statement	% who say each bothers them "a lot"
The cost of ads makes Rx drugs too expensive	77%	41%
Ads for Rx drugs encourage people to take medicine they don't need	66%	34%
There are too many Rx drug ads on television	68%	27%
Many Rx drug ads are too sexually explicit	46%	20%

Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2006)

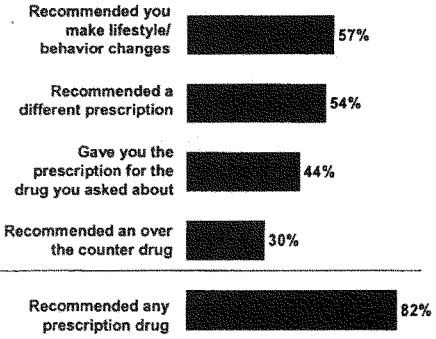
Figure 12

Outcome of Talking to a Doctor as a Result of Ads

As a result of seeing an ad for a prescription medicine, have you ever talked with a doctor about the specific medicine you saw or heard advertised, or not?



Among the 32% who have talked to a doctor as a result of seeing an Rx drug ad: Percent who say the doctor did one or more of the following...

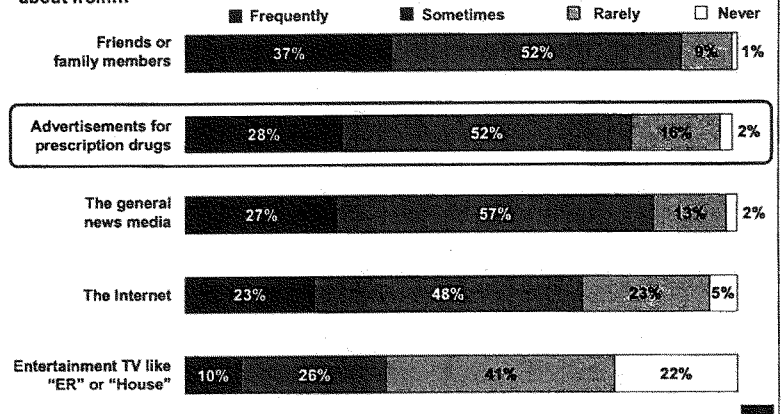


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (Jan. 3-23, 2006)

Figure 13

Physicians' Reports of Patients Asking About Rx Drugs They've Seen Advertised

How often do patients talk with you about specific diseases or treatments they heard about from...

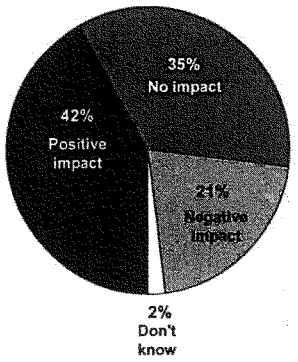


Source: Kaiser Family Foundation *National Survey of Physicians* (April 25-July 8, 2006) [Note: "Don't know" responses not shown]

Figure 14

Physicians' Opinions of Patient Inquiries from Ads and Other Sources

Overall, do you think these inquiries from patients have a positive or negative impact on your interactions with patients, or do they have no effect?

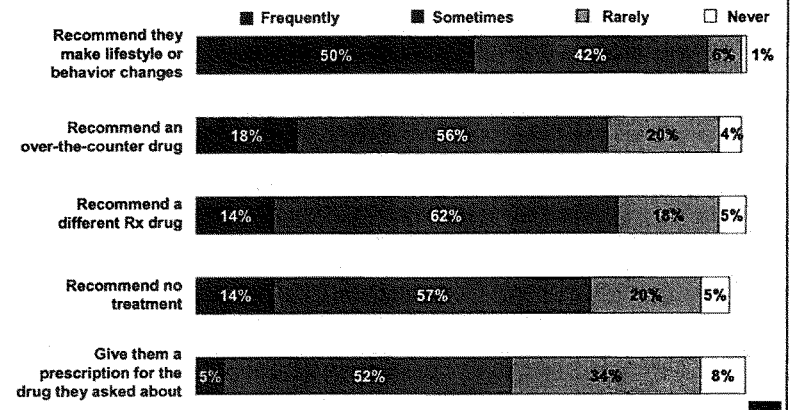


Source: Kaiser Family Foundation *National Survey of Physicians* (April 25-July 8, 2006)

Figure 15

Physicians' Reported Actions When Patients Inquire About Prescription Drugs

When a patient talks to you about a specific treatment they heard about from the media or other sources, how often do you...



Source: Kaiser Family Foundation *National Survey of Physicians* (April 25-July 8, 2006) [Note: "Don't know" responses not shown]

Mr. STUPAK. Thank you. Dr. Crosse from the Government Accountability Office, your testimony, please.

STATEMENT OF MARCIA G. CROSSE, PH.D., DIRECTOR, HEALTHCARE, GOVERNMENT ACCOUNTABILITY OFFICE

Ms. CROSSE. Thank you. Mr. Chairman and members of the subcommittee, I am pleased to be here as you examined the practice of direct-to-consumer advertising of prescription drugs. My remarks today are primarily based on our November 2006 report on trends in FDA's oversight of direct-to-consumer advertising.

As we have heard, FDA regulates the promotion and advertising of prescription drugs, including television, magazine, and Internet materials, to ensure they are not false or misleading. Drug companies do not have to obtain FDA's review of consumer advertising materials before they are disseminated. Companies sometimes voluntarily choose to submit draft versions of the materials to FDA for advisory comments in advance of public distribution. However, except in limited cases, companies are only required to submit final materials to FDA at the same time as they begin dissemination to the public.

We found that FDA reviews only a small portion of the materials it receives, and the Agency cannot ensure that identifies for review the materials it considers to be highest priority. This has occurred at a time when the number of materials for consumers has more than doubled in 5 years, to over 21,000 items in 2007. Previously, FDA officials told us that the Agency prioritizes the review of materials with the greatest potential to negatively affect public health, but there were no documented criteria for making this determination. FDA tells us that it now has developed criteria to prioritize reviews, as we recommended in 2006. However, just as we previously reported, FDA still does not systematically apply these criteria to identify the highest priority materials for review.

So what happens if the reviewers find a problem with an ad? If FDA identifies a violation, the Agency may issue a regulatory letter, asking the drug company to pull the ad or take other actions. However, since the 2002 policy change requiring internal legal review by FDA's Office of Chief Counsel of all draft regulatory letters, FDA's process for drafting and issuing letters has taken longer, and the Agency has issued fewer letters per year. Prior to this policy change, from 1997 to 2001, it took FDA an average of 2 weeks to issue a letter. By 2007, the time had increased to over 6 months. FDA officials told us that the policy change was the primary factor contributing to the longer time.

Not only did the policy change create delays, but after the policy change FDA issued many fewer of these regulatory letters. The agency issued 15 to 25 letters per year before the policy change, but only issued two such letters in 2007. FDA officials told us that the Agency does not issue letters for all violative materials that it identifies. Instead, it focuses on those that it considers the most serious and most likely to negatively affect consumers' health. At the time of our 2006 report, we found that the effectiveness of FDA's regulatory letters at halting violative ads had been limited. By the time these regulatory letters were issued, drug companies had already discontinued more than half of these ads. Generally, compa-

nies have complied with FDA requests and regulatory letters. They have removed cited materials that were still being disseminated, and those companies requested to issue corrective materials did so.

However, FDA's issuance of regulatory letters did not always prevent similar violations for the same drugs. We found that almost one-third of drugs cited had received multiple regulatory letters, sometimes for similar types of violations.

In conclusion, given substantial growth in direct-to-consumer advertising in recent years, FDA's role in limiting the dissemination of false or misleading advertising to the American public has become increasingly important. Fulfilling this responsibility requires that the Agency, among other things, review those advertising materials that are high priority and take timely action to limit the dissemination of those that are false or misleading. FDA's development of documented criteria to prioritize its reviews is a step in the right direction. However, as we recommended in 2006, we believe that FDA should take the next step of systematically applying those criteria to the materials it receives.

Finally, despite FDA agreeing with an earlier GAO recommendation in 2002 to issue regulatory letters more quickly, the amount of time it takes to draft and issue letters has continued to lengthen. We believe that delays in issuing regulatory letters limit FDA's effectiveness in overseeing direct-to-consumer ads and in reducing consumers' exposure to false and misleading ads. Mr. Chairman, this completes my prepared remarks. I would be happy to respond to any questions you or other members of the subcommittee may have.

[The prepared statement of Ms. Crosse follows:]

United States Government Accountability Office

GAO

Testimony
Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

For Release on Delivery
Expected at 10:00 a.m. EDT
Thursday, May 8, 2008

PRESCRIPTION DRUGS

Trends in FDA's Oversight of Direct-to-Consumer Advertising

Statement of Marcia Crosse
Director, Health Care



GAO-08-758T

GAO
Accountability · Integrity · Reliability

Highlights

Highlights of GAO-08-758T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

May 8, 2008

PRESCRIPTION DRUGS

Trends in FDA's Oversight of Direct-to-Consumer Advertising

Why GAO Did This Study

The Food and Drug Administration (FDA) is responsible for overseeing direct-to-consumer (DTC) advertising of prescription drugs, which includes a range of media, such as television, magazines, and the Internet. If FDA identifies a violation of laws or regulations in a DTC advertising material, the agency may issue a regulatory letter asking the drug company to take specific actions. In 2002, GAO reported on delays in FDA's issuance of regulatory letters.

GAO was asked to discuss trends in FDA's oversight of DTC advertising and the actions FDA has taken when it identifies violations. This statement is based on GAO's 2006 report, *Prescription Drugs: Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising*, GAO-07-54 (November 16, 2006). In this statement, GAO discusses the (1) DTC advertising materials FDA reviews, (2) FDA's process for issuing regulatory letters citing DTC advertising materials and the number of letters issued, and (3) the effectiveness of FDA's regulatory letters at limiting the dissemination of false or misleading DTC advertising.

For its 2006 report, GAO examined FDA data on the advertising materials the agency received and reviewed the regulatory letters it issued citing prescription drug promotion from 1997 through 2005. For this statement, GAO also reviewed data from FDA to update selected information from the 2006 report.

To view the full product, including the scope and methodology, click on GAO-08-758T. For more information, contact Marcia Crosse, (202) 512-7114, crossem@gao.gov.

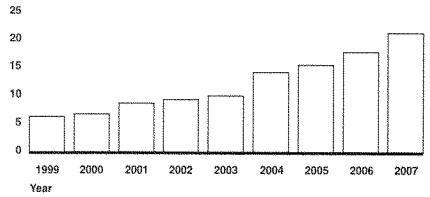
What GAO Found

Since 1999, FDA has received a steadily increasing number of advertising materials directed to consumers. In 2006, GAO found that FDA reviewed a small portion of the DTC materials it received, and the agency could not ensure that it was identifying for review the materials it considered to be highest priority. While FDA officials told GAO that the agency prioritized the review of materials that had the greatest potential to negatively affect public health, the agency had not documented criteria to make this prioritization. GAO recommended that FDA document and systematically apply criteria for prioritizing its reviews of DTC advertising materials. In May 2008, FDA indicated that it had documented criteria to prioritize reviews. However, FDA still does not systematically apply its criteria to all of the DTC materials it receives. Furthermore, GAO noted in its 2006 report that FDA could not determine whether a particular material had been reviewed. GAO recommended in that report that the agency track which DTC materials had been reviewed. FDA officials indicated to GAO in May 2008 that the agency still did not track this information. As a result, the agency cannot ensure that it is identifying and reviewing the highest-priority materials.

GAO found in 2006 that, since a 2002 policy change requiring legal review of all draft regulatory letters, FDA's process for drafting and issuing letters was taking longer and the agency was issuing fewer letters per year. FDA officials told GAO that the policy change contributed to the lengthened review.

In 2006, GAO found that the effectiveness of FDA's regulatory letters at halting the dissemination of violative DTC materials had been limited. By the time the agency issued regulatory letters, drug companies had already discontinued use of more than half of the violative advertising materials identified in each letter. In addition, FDA's issuance of regulatory letters had not always prevented drug companies from later disseminating similar violative materials for the same drugs.

Number of Materials Directed to Consumers Submitted to FDA, 1999 through 2007
Numbers in thousands



Source: GAO analysis of FDA data.

Note: Totals include final DTC materials, Internet materials—some of which may be directed to medical professionals—and materials designed to be given to consumers by medical professionals.

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today as you examine the practice of direct-to-consumer (DTC) advertising of prescription drugs, which includes a range of media, such as television, magazines, and the Internet. The Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) regulates the promotion and advertising of prescription drugs, including DTC materials, to ensure they are not false or misleading and otherwise comply with applicable laws and regulations. This oversight function is carried out by FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC). Recently, you have raised concerns regarding potentially misleading DTC advertising for several drugs.

FDA regulations require that drug companies submit final DTC advertising materials to FDA at the time they are first disseminated to the public.[1] In addition, although generally not required to do so, drug companies may voluntarily submit draft versions of DTC advertising materials to FDA for advisory comments.[2,3] If FDA identifies a violation in a disseminated DTC advertisement, such as a false or misleading safety or effectiveness claim, the agency may issue a regulatory letter. In these letters, FDA asks drug companies to take specific actions, such as stopping the dissemination of the advertisement and, if FDA finds the violation to be particularly serious, running another advertisement to correct misleading impressions left by the violative advertisement. DDMAC drafts these regulatory letters, which are then reviewed and approved by the agency's Office of Chief Counsel (OCC). In October 2002, we reported on delays in FDA's issuance of these regulatory letters and recommended that the agency take action to reduce the amount of time for internal review of draft regulatory letters citing

[1]21 C.F.R. § 314.81(b)(3)(i)(2007).

[2]21 C.F.R. § 202.1(j)(4)(2007). The FDA Amendments Act of 2007 provided FDA with new authorities related to the oversight of DTC advertising. The Act, among other things, authorizes FDA to require the submission of any draft television drug advertisement for review up to 45 days before it is scheduled to be disseminated. See Pub. L. No. 110-85, § 901(d)(2), 121 Stat. 823, 939 (2007), *codified* at 21 U.S.C. § 353b.

[3]The Pharmaceutical Research and Manufacturers of America (PhRMA) issued guidance effective January 2006 that states that "[drug] companies should submit all new DTC television drug advertisements to the FDA before releasing these advertisements for broadcast." *PhRMA Guiding Principles: Direct to Consumer Advertisements about Prescription Medicines* (Washington, D.C.: PhRMA, November 2005), http://www.phrma.org/files/DTCGuidingprinciples.pdf (accessed Apr. 29, 2008).

violations in DTC materials.[4] In response to our recommendation, FDA agreed to take steps to reduce the time to issue regulatory letters.

My remarks today are primarily based on our November 2006 report on trends in FDA's oversight of DTC advertising and the actions it took when it identified a violation in a disseminated DTC advertisement.[5] Today, I will discuss (1) the DTC advertising materials FDA reviews, (2) FDA's process for issuing regulatory letters citing DTC advertising materials and the number of letters issued, and (3) the effectiveness of FDA's regulatory letters at limiting the dissemination of false or misleading DTC advertising.

For our November 2006 report, to examine the DTC advertising materials that FDA reviewed, we obtained data from FDA on the number and type of advertising materials that it received and reviewed from 1997 through 2005. To examine FDA's process for issuing regulatory letters that cited violative DTC advertising materials and the number of such letters that FDA issued, we reviewed all regulatory letters issued by FDA from 1997 through 2005. To examine the effectiveness of these regulatory letters, we reviewed their content to identify violations cited; we did not evaluate the appropriateness or legal sufficiency of these letters. In addition, we obtained information from FDA about the timeliness of the letters issued in 2004 and 2005 and drug companies' compliance with any corrective action requested by FDA. For this statement, we reviewed data from FDA to update selected information from our 2006 report. We shared the updated facts contained in this statement with FDA officials. They provided technical comments which we incorporated as appropriate. We conducted the work for our November report from January 2006 through November 2006 and for this statement from April 2008 through May 2008. We conducted all of our work in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

[4]GAO, *Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations*, GAO-03-177 (Washington, D.C.: Oct. 28, 2002).

[5]GAO, *Prescription Drugs: Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising*, GAO-07-54 (Washington, D.C.: Nov. 16, 2006).

In summary, in our 2006 report we found that FDA reviewed a small portion of the DTC materials it received, and the agency could not ensure that it identified for review the materials it considered to be highest priority. We found that the number of final DTC materials FDA received each year had almost doubled from 2002 through 2005. Since 2006, the number of materials received by FDA has continued to increase. While FDA officials told us that the agency prioritized the review of materials that had the greatest potential to negatively affect public health, we found that the agency had not documented criteria to make this prioritization. Rather, FDA officials identified informal criteria that reviewers considered when identifying materials for review. We recommended that FDA document and systematically apply criteria for prioritizing its reviews of DTC advertising materials. We also noted in our 2006 report that FDA could not determine whether a particular material had been reviewed. Therefore, we recommended in our 2006 report that the agency track which DTC materials have been reviewed. In May 2008, FDA informed us that it now had documented criteria to prioritize reviews. However, FDA still does not systematically apply its criteria to all of the DTC materials it receives to determine which are highest priority for review. FDA officials also indicated to us in May 2008 that the agency still does not track whether a particular material has been reviewed. As a result, the agency cannot ensure that it is identifying and reviewing the highest-priority materials.

Since a 2002 policy change requiring internal legal review of all draft regulatory letters, FDA's process for drafting and issuing letters has taken longer and the agency issued fewer letters per year. Prior to this policy change, from 1997 through 2001, it took FDA an average of 2 weeks to issue a letter. After the change, from 2002 through 2005, once the agency began drafting a regulatory letter for violative DTC materials, it took an average of 4 months to issue the letter. In 2006 and 2007, the time increased to an average of over 5 months. FDA officials told us that the policy change contributed to the lengthened review by creating additional levels of review and making it necessary for the DDMAC reviewers who draft the regulatory letters to do substantially more work to prepare for and respond to comments from OCC. After the policy change, FDA issued about half as many regulatory letters that cited violative DTC advertisements per year—between 8 and 11 letters annually from 2002 through 2005, compared with 15 to 25 letters annually from 1997 through 2001. FDA issued 4 such letters in 2006 and 2 in 2007. FDA officials told us that the agency issued letters only for the violative DTC materials that it considered the most serious and most likely to negatively affect consumers' health.

At the time of our 2006 report, we found that the effectiveness of FDA's regulatory letters at halting the dissemination of violative DTC materials had been limited. FDA issued 19 such regulatory letters from 2004 through 2005. On average, it issued these letters 8 months after the violative materials were first disseminated. By the time these regulatory letters were issued, drug companies had already discontinued more than half of the violative advertisements. Generally, companies complied with FDA requests to remove cited materials that were still being disseminated, and those companies requested to issue corrective materials did so, but not until 5 months or more after the regulatory letter was issued. FDA's issuance of regulatory letters did not always prevent drug companies from later disseminating similar violative materials for the same drugs. We found that of the 89 drugs for which FDA cited violative DTC materials from 1997 through 2005, 25 drugs had DTC materials cited in more than one regulatory letter, sometimes for similar types of violations. Delays in issuing regulatory letters limit FDA's effectiveness in overseeing DTC advertising and in reducing consumers' exposure to false and misleading advertising.

Background

FDA regulates the content of all prescription drug advertising, whether directed to consumers or medical professionals. Advertising that is targeted to consumers includes both DTC and "consumer-directed" materials. DTC advertising includes, for example, broadcast advertisements (such as those on television and radio), print advertisements (such as those in magazines and newspapers), and Internet advertisements (such as consumer advertising on drug companies' Web sites). In contrast, consumer-directed advertisements are designed to be given by medical professionals to consumers and include, for example, patient brochures provided in doctors' offices.

Advertising materials must contain a "true statement" of information including a brief summary of side effects, contraindications, and the effectiveness of the drug.[6] To meet this requirement, advertising materials must not be false or misleading, must present a fair balance of the risks and benefits of the drug, and must present any facts that are material to the use of the drug or claims made in the advertising. With the exception

[6]21 C.F.R. § 202.1(e)(1),(2)(2007). Those advertising materials that call attention to the name of the drug but do not include indication or dosage recommendations for use of the drug are exempt from these brief summary requirements.

of broadcast advertisements, materials must present all of the risks described in the drug's approved labeling. Broadcast materials may present only the major side effects and contraindications, provided the materials make "adequate provision" to give consumers access to the information in the drug's approved or permitted package labeling.[7]

Within FDA, DDMAC is responsible for implementing the laws and regulations that apply to prescription drug advertising. In March 2002, DDMAC created a DTC Review Group, which is responsible for oversight of advertising materials that are directed to consumers. As of May 2008, the group had a total of two group leaders, seven reviewers, and two social scientists. This group's responsibilities include reviewing final DTC materials and reviewing and providing advisory comments on draft DTC materials. The group also monitors television, magazines, and consumer advertising on drug companies' Web sites to identify advertising materials that were not submitted to FDA at the time they were first disseminated and reviews advertising materials cited in complaints submitted by competitors, consumers, and others.

Once submitted to FDA, final and draft DTC advertising materials are distributed to a DTC reviewer. For final materials, if the reviewer identifies a concern, the agency determines whether it represents a violation and merits a regulatory letter. For draft materials submitted by drug companies, FDA may provide the drug company with advisory comments to consider before the materials are disseminated to consumers if, for example, the reviewers identify claims in materials that could violate applicable laws and regulations.

If FDA identifies violations in disseminated DTC materials, the agency may issue two types of regulatory letters—either a "warning letter" or an "untitled letter." Warning letters are typically issued for violations that may lead FDA to pursue additional enforcement actions if not corrected; untitled letters are issued for violations that do not meet this threshold. Both types of letters cite the type of violation identified in the company's

[7]FDA published draft guidance for DTC broadcast advertisements in 1997, and final guidance in 1999, that described an approach drug companies could use to meet the regulatory requirement for making adequate provision of key information. The outlined approach provides that drug companies disseminate complete information included in a drug's approved package labeling through alternative sources, such as a toll-free number and a drug company Web site. See FDA, *Guidance for Industry: Consumer-Directed Broadcast Advertisements* (Rockville, Md.: Aug. 1999).

advertising material, request that the company submit a written response to FDA within 14 days, and request that the company take specific actions. Untitled letters request that companies stop disseminating the cited advertising materials and other advertising materials with the same or similar claims. Warning letters further request that the company issue advertising materials to correct the misleading impressions left by the violative advertising materials.[8] The draft regulatory letters are subsequently reviewed by officials in DDMAC, FDA's Office of Medical Policy (which oversees DDMAC), and OCC. FDA has stated that it instituted OCC review for the purpose of promoting voluntary compliance by ensuring that drug companies that receive a regulatory letter understand that the letter has undergone legal review and the agency is prepared to go to court if necessary.[9]

FDA Reviewed a Small Portion of DTC Materials and Could Not Ensure It Was Reviewing the Highest-Priority Materials

As of 2006, FDA reviewed a small portion of the increasingly large number of DTC materials it received. FDA attempted to target available resources by focusing its reviews on the DTC advertising materials that had the greatest potential to negatively affect public health, but the agency did not document criteria for prioritizing the materials it received for review. Agency reviewers considered several informal criteria when prioritizing the materials, but these were not systematically applied and the agency did not document if a particular DTC material was reviewed. As a result, the agency could not ensure that it was identifying or reviewing the materials that were the highest priority.

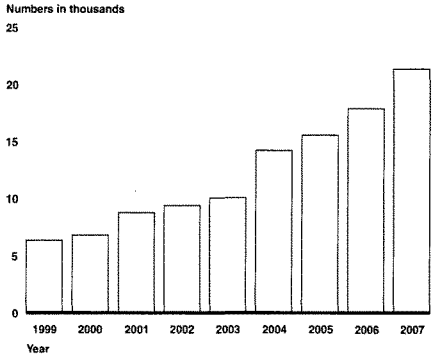
FDA officials told us at the time of our 2006 report that the agency received substantially more final and draft materials than the DTC Review Group could review. In 2005, FDA received 4,600 final DTC materials

[8]While FDA does not have explicit authority to require companies to act upon these letters, if the companies continue to violate applicable laws or regulations, the agency has other administrative and judicial enforcement avenues that could encourage compliance or result in the product being taken off the market. For example, FDA, through the Department of Justice, may seek additional remedies in the courts resulting in the seizure of drugs deemed to be misbranded because their advertising is false or misleading. With the enactment of the FDA Amendments Act of 2007, FDA was also authorized to assess civil monetary penalties. Pub. L. No. 110-85, § 901(d)(4), 121 Stat. 823, 940-942 (2007), *codified* at 21 U.S.C. § 333(g).

[9]See GAO-03-177, 32.

(excluding Internet materials) and 6,168 final Internet materials.[10] FDA also received 4,690 final consumer-directed materials—such as brochures given to consumers by medical professionals. FDA received a steadily increasing number of final materials from 1999 through 2005. We found that, in 2006 and 2007, the total number of final DTC, Internet, and consumer-directed materials FDA received continued to increase.[11] (See fig. 1.)

Figure 1: Number of Final DTC, Internet, and Consumer-Directed Materials Submitted to FDA, 1999 through 2007



Source: GAO analysis of FDA data.

[10]FDA's count of submitted materials did not distinguish between Internet materials targeted to consumers and those targeted to medical professionals. However, FDA officials told us that most Internet materials, such as drug companies' Web sites, include both a consumer and a professional component.

[11]We could not determine whether there had been a similar increase in the number of draft DTC materials FDA received because the agency did not track this information.

FDA officials estimated that reviewers spent the majority of their time reviewing and commenting on draft materials. However, we were unable to determine the number of final or draft materials FDA reviewed, because FDA did not track this information. In the case of final and draft broadcast materials, FDA officials told us that the DTC group reviewed all of the materials it received; in 2005, it received 337 final and 146 draft broadcast materials. However, FDA did not document whether these or other materials it received had been reviewed. As a result, FDA could not determine how many materials it reviewed in a given year. We recommended in our 2006 report that the agency track which DTC materials had been reviewed. FDA officials indicated to us in May 2008 that the agency still did not track this information.

At the time of our 2006 report, FDA officials identified informal criteria that the agency used to prioritize its reviews. FDA officials told us that, to target available resources, the agency prioritized the review of the DTC advertising materials that had the greatest potential to negatively affect public health. We recommended that FDA document its criteria for prioritizing its reviews of DTC advertising materials. FDA informed us in May 2008 that it now has documented criteria to prioritize reviews. For example, its first priority is to review materials with "egregious" violations, such as those identified through complaints. In addition, FDA places a high priority on reviewing television advertising materials. FDA officials also told us that the agency places a high priority on reviewing draft materials because they provide the agency with an opportunity to identify problems and ask drug companies to correct them before the materials are disseminated to consumers.

We reported in 2006 that FDA did not systematically apply its criteria for prioritizing reviews to all of the materials that it received. Specifically, we found in 2006 that, at the time FDA received the materials, it recorded information about the drug being advertised and the type of material being submitted but did not screen the DTC materials to identify those that met its various informal criteria. FDA officials told us that the agency did identify all final and draft broadcast materials that it received, but it did not have a system for identifying any other high-priority materials. Absent such a system for all materials, FDA relied on each of the reviewers—in consultation with other DDMAC officials—to be aware of the materials that had been submitted and to accurately apply the criteria to determine the specific materials to review. This created the potential for reviewers to miss materials that the agency would consider to be a high priority for review. Furthermore, because FDA did not track information on its reviews, the agency could not determine whether a particular material had

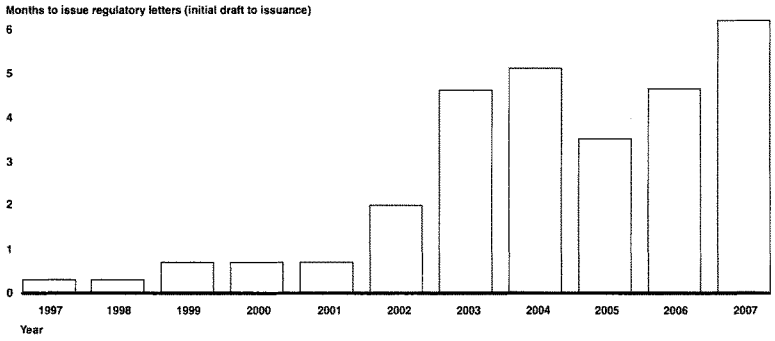
been reviewed. As a result, the agency could not ensure that it identified and reviewed the highest-priority materials. We recommended that the agency systematically screen the DTC materials it received against its criteria to identify those that are the highest priority for review. As of May 2008, FDA still did not have such a process.

After the 2002 Policy Change, FDA's Process for Issuing Regulatory Letters Took Longer and the Number of Letters Issued Declined

In 2006 we reported that, after the 2002 policy change requiring legal review by OCC of all draft regulatory letters, the agency's process for drafting and issuing letters citing violative DTC materials had stretched to several months and FDA had issued fewer regulatory letters per year. As a result of the policy change, draft regulatory letters received additional levels of review and the DTC reviewers who drafted the letters did substantially more work to prepare for and respond to comments resulting from review by OCC. FDA officials told us that the agency issued letters for only the violative DTC materials that it considered the most serious and most likely to negatively affect consumers' health.

Once FDA identified a violation in a DTC advertising material and determined that it merited a regulatory letter, FDA took several months to draft and issue a letter. For letters issued from 2002 through 2005, once DDMAC began drafting the letter for violative DTC materials it took an average of about 4 months to issue the letter. The length of this process varied substantially across these regulatory letters—one letter took around 3 weeks from drafting to issuance, while another took almost 19 months. In comparison, for regulatory letters issued from 1997 through 2001, it took an average of 2 weeks from drafting to issuance. We recommended in 2002 that the agency reduce the amount of time to draft and issue letters and the agency agreed. We found in 2006, however, that the review time had increased and we again urged the agency to issue the letters more quickly. In 2006 and 2007, it took an average of more than 5 months from drafting to issuance. One letter took less than 2 months to issue while another took about 11 months. (See fig. 2 for the average months from 1997 through 2007.)

Figure 2: Average Months to Issue Regulatory Letters Citing Violative DTC Materials, 1997 through 2007



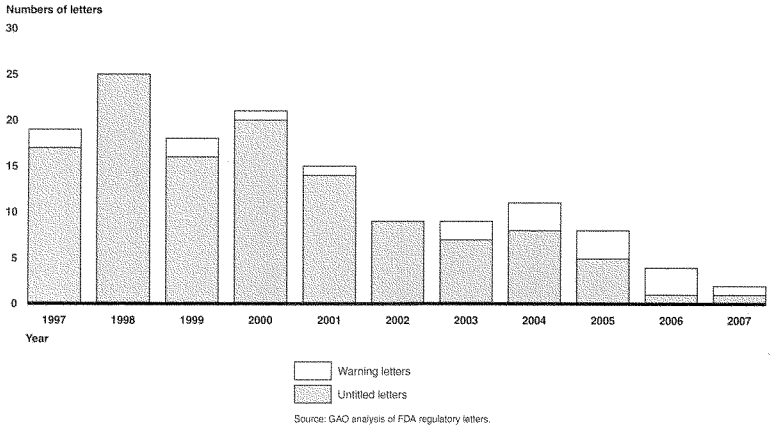
Source: GAO analysis of FDA documents.

Note: For each letter, we determined the number of months from the date on which a reviewer first began drafting a regulatory letter to the date the letter was issued. FDA does not track the date a violation was identified or the date it was determined that the violation merited a regulatory letter.

The primary factor that contributed to the increase in the length of FDA's process for issuing regulatory letters was the additional work that resulted from the 2002 policy change. All DDMAC regulatory letters were reviewed by both OCC staff and OCC's Chief Counsel. In addition to the time required of OCC, DDMAC officials told us that the policy change created the need for substantially more work on their part to prepare the necessary documentation for legal review. After meeting with OCC and revising the draft regulatory letter to reflect the comments from OCC, DDMAC would formally submit a draft letter to OCC for legal review and approval. OCC often required additional revisions before it would concur that a letter was legally supportable and could be issued. While OCC officials told us that the office had given regulatory letters that cited violative DTC materials higher priority than other types of regulatory letters, their review of DDMAC's draft regulatory letters was a small portion of their other responsibilities and had to be balanced with other requests, such as the examination of legal issues surrounding the approval of a new drug. Recently, FDA informed us that it now allows some steps to be eliminated—if deemed unnecessary for a particular letter—in an attempt to make the legal review process more efficient.

The number of regulatory letters FDA issued per year for violative DTC materials decreased after the 2002 policy change lengthened the agency's process for issuing letters. From 2002 to 2005, the agency issued between 8 and 11 regulatory letters per year that cited DTC materials. Prior to the policy change, from 1997 through 2001, FDA issued between 15 and 25 letters citing DTC materials per year. An FDA official told us that both the lengthened review time resulting from the 2002 policy change and staff turnover within the DTC Review Group contributed to the decline in the number of issued regulatory letters. More recently, we found that the number of letters issued that cite DTC materials has continued to decline—FDA issued 4 letters in 2006 and 2 letters in 2007. (See fig. 3 for the number of letters issued from 1997 through 2007.)

Figure 3: Number of Regulatory Letters FDA Issued That Cited DTC Advertising Materials, 1997 through 2007



Source: GAO analysis of FDA regulatory letters.

Although the total number of regulatory letters FDA issued for violative DTC materials has decreased, the agency has issued in recent years proportionately more warning letters—which cite violations FDA considers to be more serious. Historically, almost all of the regulatory letters that FDA issued for DTC materials were untitled letters for less serious violations. From 1997 through 2001, FDA issued 98 regulatory letters citing DTC advertising materials, 6 of which were warning letters. From 2002 through 2005, 8 of the 37 regulatory letters were warning letters. Of the 6 letters FDA issued for DTC materials in 2006 and 2007, 4 were warning letters.

FDA regulatory letters may cite more than one DTC material or type of violation for a given drug. Of the 19 regulatory letters FDA issued from 2004 through 2005, 7 cited more than 1 DTC material, for a total of 31 different materials. These 31 materials appeared in a range of media, including television, radio, print, direct mail, and the Internet. Further, FDA identified multiple violations in 21 of the 31 DTC materials cited in the letters. The most commonly cited violations related to a failure of the material to accurately communicate information about the safety of the drug. The letters also often cited materials for overstating the effectiveness of the drug or using misleading comparative claims. Of the 6 regulatory letters FDA issued in 2006 or 2007 that cited DTC materials, 2 cited more than 1 DTC material and all identified multiple violations in each of the cited materials.

For our 2006 report, FDA officials told us, that the agency issued regulatory letters for DTC materials that it believed were the most likely to negatively affect consumers and that it did not act on all of the concerns that its reviewers identified. For example, they said the agency may be more likely to issue a letter when a false or misleading material was broadly disseminated. When reviewers had concerns about DTC materials, they discussed them with others in DDMAC and may have met with OCC and medical officers in FDA's Office of New Drugs to determine whether a regulatory letter was warranted. However, because FDA did not document decisions made at the various stages of its review process about whether to pursue a violation, officials were unable to provide us with an estimate of the number of materials about which concerns were raised but the agency did not issue a letter.

Effectiveness of FDA Regulatory Letters at Halting Dissemination of Violative DTC Materials Was Limited

At the time of our 2006 report, we found that FDA regulatory letters were limited in their effectiveness at halting the dissemination of false and misleading DTC advertising materials. We found that, from 2004 through 2005, FDA issued regulatory letters an average of about 8 months after the violative DTC materials they cited were first disseminated, by which time more than half of the materials had already been discontinued. Although drug companies complied with FDA's requests to create materials to correct the misimpressions left by the cited materials, these corrections were not disseminated until 5 months or more after FDA issued the regulatory letter. Furthermore, FDA's regulatory letters did not always prevent drug companies from later disseminating similar violative materials for the same drugs.

Because of the length of time it took FDA to issue these letters, violative advertisements were often disseminated for several months before the letters were issued. From 2004 through 2005, FDA issued regulatory letters citing DTC materials an average of about 8 months after the violative materials were first disseminated. FDA issued one letter less than 1 month after the material was first disseminated, while another letter took over 3 years. The cited materials were usually disseminated for 3 or more months, and of the 31 violative DTC materials cited in these letters, 16 were no longer being disseminated by the time the letter was issued. On average, these letters were issued more than 4 months after the drug company stopped disseminating these materials and therefore had no effect on their dissemination. For the 14 DTC materials that were still in use when FDA issued the letter, the drug companies complied with FDA's request to stop disseminating the violative materials. However, by the time the letters were issued, these 14 materials had been disseminated for an average of about 7 months.[12]

As requested by FDA in the regulatory letters, drug companies often identified and stopped disseminating other materials with claims similar to those in the violative materials. For 18 of the 19 regulatory letters issued from 2004 through 2005, the drug companies indicated to FDA that they had either identified additional similar materials or that they were reviewing all materials to ensure compliance. In addition to halting materials directed to consumers, companies responding to 11 letters also

[12]For one violative advertising material, we were unable to determine from FDA's files when the violative advertising material ended.

stopped disseminating materials with similar claims that were targeted directly to medical professionals.

Drug companies disseminated the corrective advertising materials requested in FDA warning letters, but took 5 months or more to do so. In each of the six warning letters FDA issued in 2004 and 2005 that cited DTC materials, the agency asked the drug company to disseminate truthful, nonmisleading, and complete corrective messages about the issues discussed in the regulatory letter to the audiences that received the violative promotional materials. In each case, the drug company complied with this request by disseminating corrective advertising materials. For the six warning letters FDA issued in 2004 and 2005 that cited DTC materials, the corrective advertising materials were initially disseminated more than 5 to almost 12 months after FDA issued the letter. For example, for one allergy medication, the violative advertisements ran from April through October 2004, FDA issued the regulatory letter in April 2005, and the corrective advertisement was not issued until January 2006.

FDA regulatory letters did not always prevent the same drug companies from later disseminating violative DTC materials for the same drug, sometimes using the same or similar claims. From 1997 through 2005, FDA issued regulatory letters for violative DTC materials used to promote 89 different drugs. Of these 89 drugs, 25 had DTC materials that FDA cited in more than one regulatory letter, and one drug had DTC materials cited in eight regulatory letters.[13] For 15 of the 25 drugs, FDA cited similar broad categories of violations in multiple regulatory letters. For example, FDA issued regulatory letters citing DTC materials for a particular drug in 2000 and again in 2005 for "overstating the effectiveness of the drug." For 4 of the 15 drugs, FDA cited the same specific violative claim for the same drug in more than one regulatory letter. For example, in 1999 FDA cited a DTC direct mail piece for failing to convey important information about the limitations of the studies used to approve the promoted drug. In 2001, FDA cited a DTC broadcast advertisement for the same drug for failing to include that same information.

[13]In 2006 and 2007, FDA issued 6 letters for drugs that had not previously been cited in regulatory letters. As of April 2008, the agency had issued one regulatory letter for a drug that had been cited in 2 previous regulatory letters.

Concluding Observations

Given substantial growth in the number of DTC advertising materials submitted to FDA in recent years, FDA's role in limiting the dissemination of false or misleading advertising to the American public has become increasingly important. Fulfilling this responsibility requires that the agency, among other things, review those DTC advertising materials that are highest priority and take timely action to limit the dissemination of those that are false or misleading. We found in 2006 that FDA did not have a complete and systematic process for tracking and prioritizing all materials that it received for review. FDA's development of documented criteria to prioritize reviews is a step in the right direction. However, as we recommended in 2006, we believe that FDA should take the next step of systematically applying those criteria to the DTC materials it receives to determine which are highest priority for review. While the agency said that it would require vastly increased staff to systematically screen materials, we found in 2006 that FDA already has most of the information it would need to do so. Finally, despite FDA agreeing in 2002 that it is important to issue regulatory letters more quickly, the amount of time it takes to draft and issue letters has continued to lengthen. We believe that delays in issuing regulatory letters limit FDA's effectiveness in overseeing DTC advertising and in reducing consumers' exposure to false and misleading advertising.

Mr. Chairman, this completes my prepared statement. I would be happy to respond to any questions you or the other members of the subcommittee may have at this time.

Contacts and Acknowledgments

For further information about this statement, please contact Marcia Crosse, at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this statement. Martin T. Gahart, Assistant Director; Chad Davenport; William Hadley; Cathy Hamann; Julian Klazkin; and Eden Savino made key contributions to this statement.

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Congressional Relations	Ralph Dawn, Managing Director, dawnr@gao.gov, (202) 512-4400 U.S. Government Accountability Office, 441 G Street NW, Room 7125 Washington, DC 20548
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Mr. STUPAK. Well, thank you, and thank you to all of our witnesses for your testimony. We will begin questions. Dr. Nielsen, why does the AMA have policies on direct-to-consumer advertising?

Dr. NIELSEN. We have policy because physicians have been concerned about this for 20 years. We have seen a change in the legal environment. This, apparently, is protected under the First Amendment, and therefore it is unlikely that the clock will be turned back to a ban. However, as was pointed out, there are only two countries in the world that allow this kind of advertising, the other being New Zealand.

So it has been a concern, and doctors, frankly, are not real fond of direct-to-consumer advertising, not because we don't want patients to come in and talk about their symptoms. We do value the educational aspects, but it is frankly fairly clear that that the majority of what is happening has a marketing effect rather than an educational effect, and it is troubling when a patient comes in with a demand for a particular drug, and that sometimes results in what you have heard described from the Kaiser Family Foundation.

Mr. STUPAK. Would you believe that because a doctor appears in an ad the general public are more apt to believe the credibility of that ad? Is that the AMA's position?

Dr. NIELSEN. It is our position that we strongly discourage physicians from appearing in ads.

Mr. STUPAK. Why do you strongly discourage?

Dr. NIELSEN. Because we think that, frankly, they don't know the patients that they are talking to and it does lend an air of credibility. We discourage it. We say that if it does happen, then there should be a disclaimer indication that the physician has been compensated.

Mr. STUPAK. OK, so there has to be a disclaimer about compensation.

Let me talk about the Lipitor ad there with Dr. Jarvik. He is not a license doctor, right?

Dr. NIELSEN. No, but it is my understanding he does have an M.D. degree, so he would be appropriately referred to as Dr. Jarvik, although it is also my understanding he has never been licensed.

Mr. STUPAK. So he is not licensed to write a prescription for Lipitor, is he?

Dr. NIELSEN. That is correct, but once he graduated from medical school, he is a doctor.

Mr. STUPAK. OK, is he a cardiologist?

Dr. NIELSEN. It is my understanding that he is not, no. He is certainly an expert in matters involving the heart, as we all know, in terms of the device.

Mr. STUPAK. Is he a cardiac surgeon?

Dr. NIELSEN. No, sir.

Mr. STUPAK. Is it AMA's position, like when they had that person rowing in the Lipitor ad, that they should disclose that was not Dr. Jarvik?

Dr. NIELSEN. Well, actually, when I saw the ad, I didn't know it was supposed to be Dr. Jarvik. Sorry, I think that went right past me.

Mr. STUPAK. Everyone assumed it was. Sorry. What is a heart expert? They use that word in that ad. What is a heart expert?

Dr. NIELSEN. Well, there are lots of heart experts. We have physiologists at my medical school who teach cardiac physiology. They certainly are heart experts. That is very different than being a cardiologist.

Mr. STUPAK. So it could be a full-fledged cardiologist to a consumer advocate?

Dr. NIELSEN. I am sorry, I don't understand.

Mr. STUPAK. Well, it could mean almost anything then, right? Heart expert could mean almost anything. By using it in an ad, you don't know how I am referencing it.

Dr. NIELSEN. I guess that is correct. There are many people with many different kinds of expertise that could be referred to in that manner.

Mr. STUPAK. Dr. Brodie, if I may, can you tell us whether the public is interested in seeing more regulation or less regulation based upon your studies?

Ms. BRODIE. In our latest study, definitely, there is an interest from some for more regulation in this area. We found about 43 percent felt that there was a need for more regulation. About 48 percent said that there was already about the right amount.

Mr. STUPAK. Your latest study, is this the one that was in January?

Ms. BRODIE. Yes.

Mr. STUPAK. It was in USA Today. I think Kaiser had it in USA Today in early January, right?

Ms. BRODIE. Yes, it was a partnership with us, the USA Today and the Harvard School of Public Health, and the data was collected in January of 2008.

Mr. STUPAK. And if I remember correctly that data basically said that we would like to see the regulation on pricing of drugs come down, right?

Ms. BRODIE. The real complaint that the public has is not so much as the ads themselves, but it is their perceived impact that the ads have on prices. The real concern the public has about prescription drugs right now is the price of drugs. Certainly, we saw about two-thirds of people interested in seeing more regulation when it came to prices, but my take-away message from the public is that because they have become more skeptical of drug ads over time, because they are concerned about the relationship between ads and prices, and because they also give them low scores on their ability to communicate side effects, I think that regulation in this area would be welcome. I think any or any other efforts would be welcome in trying to help improve prescription drug advertising.

Mr. STUPAK. Right. In fact if I take away something from your study there, it was like, well, we think they do a decent job of advertising but the thing they sort of fall off on or don't tell us about are the side effects.

Ms. BRODIE. Yes. They gave good scores when it came to being able to communicate what the drug was for and the basic benefits of the drug. The public feels like that information is communicated well but they feel like they do a less good job talking about the side effects.

Mr. STUPAK. Dr. Nielsen mentioned that when she was taking care of her grandchild, about the inappropriateness of the ad when she was helping her grandchild. Did the public have any sentiment like that, as Congressman Hall mentioned to me earlier today on the floor. Do they think there is appropriateness when an ad should be shown and when it should not be shown?

Ms. BRODIE. Our research didn't ask exactly about the appropriateness of the timing of ads, but we did ask whether they felt like ads were too sexually explicit, and about 40 percent felt that they were, these direct-to-consumer ads could be too sexually explicit. On the other hand, this wasn't something that bothered people very much. Only about 20 percent said that that bothered them a lot. So I think that it certainly bothers some people out here, but I wouldn't say it is a general impression. But we didn't ask specifically about the timing of ads.

Mr. STUPAK. And I am sure your group had to be at least 18 or older to answer your questions.

Ms. BRODIE. Yes, it is a national random adult sample.

Mr. STUPAK. I would be interested if we could go to a preschool and see what they are saying.

Questions, Mr. Shimkus?

Mr. SHIMKUS. Thank you, Mr. Chairman. I will tell you all and the folks in the audience here that I have a major concern on the timing of these ads. Dr. Nielsen, I would concur with you, and I think my positions here over the many years support a family hour, support the appropriateness of what is broadcast. And I am just putting that out for the record because I have been in that same position, although it has not been with my grandchildren, it is with my children, since I am a late bloomer. And Dr. Day, I apologize for not being here but I would like to just publicly say I would like to have you come by and visit with me. I would like to visit the flapping of wings and the peer review issue of research. So if you could do that, I would appreciate it.

Dr. Nielsen, are you aware of the Food and Drug Administration study proposed experimental evaluation and impact distraction on consumer understanding of risk and benefit information in direct-to-consumer prescription drug broadcast advertisements published in the Federal Register on August 22, 2007?

Dr. NIELSEN. I have not read that, sir.

Mr. SHIMKUS. The purpose of the study is, in part, part of this debate, so I would encourage you to look at that, and we add that into the toolbox of understanding about this whole approach. I think it would be helpful.

Dr. NIELSEN. If I could just comment, we certainly support the FDA, as I have stated.

Mr. SHIMKUS. Do you support the provision that we increase the authority of the FDA to do civil penalties and the like with the understanding that we have done that and it has only been a short term that it has been in play.

Dr. NIELSEN. Yes, sir. And in fact, our policy goes further than what has been passed by Congress and it encourages that pre-approval, as you know.

Mr. SHIMKUS. Do you concur with the statements from my friend from California that made the assumption that we can't trust phy-

sicians because they are bought off by the pharmaceutical companies?

Dr. NIELSEN. Well, I think what you heard from Dr. Day is physicians are people like everybody else, and the way things are presented to them is just as important as the way it is presented to consumers.

Mr. SHIMKUS. So you agree with him?

Dr. NIELSEN. I agree that physicians are people. I do not agree that physicians are bought off by drug companies.

Mr. SHIMKUS. Well, I mean that is the assertion made.

Dr. NIELSEN. I heard that, sir. I was in the audience. We have an ethical position about that that we would be happy to discuss with you.

Mr. SHIMKUS. I'm fine with your position. I think I would address it with my colleague from California. I think that is who made the assertion. I appreciate your profession. I appreciate the Hippocratic Oath. I think part of this problem is the prescriber of the drug is whom?

Dr. NIELSEN. Drugs are prescribed by physicians. They can also be prescribed, in some states, by other health professionals.

Mr. SHIMKUS. So the health professionals do the prescribing and part of the Kaiser Foundation research said that one of the benefits is it helps create information for people to go to physicians. And really, in the Kaiser study, it said that on the most part that doctors directed these patients who came for information to other drugs or lifestyle changes. You would think that that would beneficial, wouldn't you?

Dr. NIELSEN. Indeed. And in fact, when a patient comes in discussing symptoms, that can only be a good thing.

Mr. SHIMKUS. And I think, again, that is the debate, especially with the First Amendment issues. Again, my caveat is this family hour provision and the timeliness of advertising, which might claim that I am schizophrenic on this, but I think when it comes to the kids and what is aired over the air, I am willing to really push that issue.

Dr. NIELSEN. The ethical tenets of our profession are very clear, that one should, in prescribing a drug, do what is best for that patient. There is no question about that.

Mr. SHIMKUS. Dr. Crosse, you are aware that the Congress increased spending on staff assigned to review ads to $6.25 million a year from the previous high of just over $1 million?

Ms. CROSSE. Yes, I believe under the amendments act.

Mr. SHIMKUS. Have you staffed up?

Ms. CROSSE. The FDA has increased the staff assigned to the division to review these ads.

Mr. SHIMKUS. So we have new law and we have increased staffing, so we are moving in the right direction if we are concerned about direct-to-consumer marketing.

Ms. CROSSE. I would believe that there are number of steps that are positive in this area.

Mr. SHIMKUS. You mentioned a change in policy with regard to review of regulatory letters so that the chief counsel's office reviews them for legal sufficiency. Why was this change made?

Ms. CROSSE. We don't really have a clear understanding of why this specific change was made. We reported on it in 2002 and again in 2006. I think there was a concern that came down from HHS from the General Counsel's office direction that this change be made to review the letters for sufficiency.

Mr. SHIMKUS. Thank you. Mr. Chairman.

Mr. STUPAK. Mr. Barton for questions. Do you want to do an opening statement?

Mr. BARTON. I shall just take five minutes and going to do a little of both since I have been delayed.

I apologize for not being here for a good part of the hearing. As we all know, there have been a lot of votes on the floor and things like that, but you know, last year, the committee, on a bipartisan basis, adopted an amendment to give the FDA some new authority in terms of making sure that drug ads are done properly. I don't know if there have been any questions about that. But we are in a situation today—this is not, in my opinion, Sinclair Lewis of the early 1900s when we had buyer-beware drugs and food products being sold to the American people. One of the drugs that is under review today I take: Lipitor. I have taken it for 2 years since I had a heart attack. I go see my cardiologist every 6 months, and according to him, it is working fine, and I am working fine.

So I guess I would ask our AMA witness, Dr. Nielsen, do you consider some of these drug ads to be so misleading that we should consider changing the current laws we have for reviewing them at the FDA?

Dr. NIELSEN. Yes, sir. As I stated in my testimony, it is AMA policy that the FDA be given authority, and of course by that we mean effective authority to not only do the kind of sanctioning that has already been granted to them, but also to give them the authority and the resources to carry out the mission to pre-approved direct-to-consumer ads.

Mr. BARTON. So you think this is a more important problem than plants in China that are putting poison into heparin?

Dr. NIELSEN. No, sir, that is not at all what we mean. The FDA has wide authority. But as long as it is legal to do direct-to-consumer drug advertisements, then it is very important that it not be misleading to the public. So as long as we have it, there has to be regulation.

Mr. BARTON. These ads that we are reviewing today were aired before the new law that we passed last year and the new regulation had actually been implemented. And as I understand it, most of the ads that are in question today have been voluntarily pulled from television. So I just want to make sure I understand, it is the American Medical Association position that current law that has yet to have the regulations implemented is not strong enough.

Dr. NIELSEN. That is our policy, and it is not targeted against any specific ads.

Mr. BARTON. Mr. Chairman, I respectfully disagree with the AMA's position, but I respect the American Medical Association. I will be happy to look at the issue in greater detail. I don't consider this to be the most pressing issue that is before the subcommittee. And as you know, since I used to chair this subcommittee, I am a strong supporter of aggressive oversight and investigation, and I

will support you and Chairman Dingell procedurally in almost anything that you wish to investigate. But I would hope that some of the other issues that were ongoing, including our foreign food inspections, would perhaps take a little bit higher priority. With that, I yield back.

Mr. STUPAK. I thank the gentleman. While it is true there are new rules, which some of us think are very weak provisions, but they are new provisions, and I hope that these hearings not only highlight the fact there are some new rules that will be implemented, but maybe FDA will take it seriously, Number one. Number two, apply pressure on the FDA to quickly enact these new rules and not take years to do it, and take actions against violators. So those are some of the reason why we are doing this. On a lighter note, I notice that you have been taking Lipitor for 2 years, do we expect to see you on the Potomac rowing?

Mr. BARTON. Well, I have got as much experience doing that as the person that was in the ad.

Mr. STUPAK. I think you have more experience. But on a serious note, I think it is the first time we have had an opportunity to take note of your portrait, and I would like to congratulate you on having that addition of your portrait in the hearing room as former chair, so thank you and thank you for being here.

Mr. Whitfield, I guess, for question. And we will go another round. I have questions, and we will go another round.

Mr. WHITFIELD. Thank you, Mr. Chairman, and I thank the panel for being here. I am sorry I missed your testimony, but I am a little bit familiar with what your testimony was.

Dr. Nielsen, recognizing that the AMA's position is pre-clearance of these ads, it is my understanding that you have made some reference that direct-to-consumer ads may cause or contribute to overutilization of prescription drugs. Is that your position or is that correct?

Dr. NIELSEN. That is our concern. We respectfully request studies to look at that.

Mr. WHITFIELD. OK, but there have been no studies on that?

Dr. NIELSEN. There have been some, as you have heard, that have approached it in other ways, but it is a concern, as everyone is worried about healthcare costs, particularly if the advertising is for drugs that are under patent, which may be no more effective than a drug that is available that is considerably cheaper.

Mr. WHITFIELD. Well, the thing that puzzles me about all of this, and I talked a little bit about this in my opening statement is the fact that the doctor prescribes the medicine, and that is what they are trained to do, to diagnose and prescribe the medicine. So are you saying that doctors are actually influenced by their patients because of what patients see on television about ads?

Dr. NIELSEN. I think there is no question that that is the case, and it causes some problematic moments in the office. I can tell you, absolutely, from my own 23 years in practice that it happened periodically. It happened several times a week. Patients came in, essentially convinced because, particularly a television ad convinced them that they needed a specific drug. So the conversation, then, was not about the symptoms so much as it was about why that drug or some alternative was going to be——

Mr. WHITFIELD. So what is the responsibility of the doctor in that instance?

Dr. NIELSEN. The responsibility is very clear. The doctor's ethical responsibility is to do what he or she thinks is the best thing for that patient. When there are alternatives, it is, in fact, quite possible that the physician may be persuaded by the patient's increased demand that as one of the alternatives be prescribed, but it always has to be in the patient's best interest.

Mr. WHITFIELD. I know that it is difficult to speak categorically in every instance, but generally speaking, it has been my experience that when I go to a doctor or when family members go to a doctor, and when I served on the health subcommittee, that generally speaking, patients listen to their doctors, and generally speaking, they are pretty comfortable with the physician's opinion. They may go out and get a second opinion or a third opinion, which I think is good, but I would just be shocked, myself, to think that physicians would be so intimidated or pressured by patients to prescribe a particular drug because of someone seeing it on television. And maybe I am being naive, but I just feel like one of the problems in our healthcare system, in my view, is that patients, generally, almost categorically do what the doctor says and that they should get a second opinion or so. Do you think I am off base in that belief or not?

Dr. NIELSEN. No, not completely, but let me offer a couple of things. First, you heard from the Kaiser Family Foundation, and I will defer to my colleague to give us the statistics, but you heard that about half of the time the physician will prescribe something else or recommend an alternative, or sometimes an over-the-counter approach. On the other hand, there are other studies which show that a patient may leave a physician if they do not get the drug that they are seeking, and every doctor will tell you about that. That doesn't mean that they give them the drug so they don't leave, but they have had patients leave them, so think it is not quite true that all patients do what their doctors recommend. Would that it were so and would that we had better communication between patients and doctors about their symptoms.

Mr. WHITFIELD. In this information age in which we live today, with the Internet and people go online and put in drugs and all sorts of information is available, I don't have any scientific evidence to support this, but I would imagine that people can go on the Internet and get all sorts of information about drugs that maybe they are getting as much information from that source as they are from direct ads. Is that any concern to you about all of the information that is out there on the Internet?

Dr. NIELSEN. In my experience, most of the time the Internet research done is more disease-specific than drug-specific. It does lead people, sometimes, to the drug-specific information. However, what we are really talking about today is the ads, primarily on television, because that has been relatively new over the past 11 years. The print ads tend to be a little more balanced, but the TV ads are the ones that are of more concern, and that is different than a patient searching for information about diabetes on the Internet. You are absolutely right you can get good and bad information on the Internet as well.

Mr. WHITFIELD. Dr. Crosse, two of the three ad campaigns we are discussing with the next panel involve direct-to-consumer advertising on treatment options for high cholesterol. Did your November 2006 report on direct-to-consumer ads recognize any beneficial relationship between those direct-to-consumer ads and treating high cholesterol?

Ms. CROSSE. Yes, we talked in that report about the research that is out there that talks about the role of these ads in informing and educating patients as well as some of the same concerns that we have just heard from Dr. Nielsen. There has been research on both sides of this issue, and there certainly is some evidence that it can play a positive role in informing patients about treatment options they may not have been aware of before.

Mr. WHITFIELD. I see my time has expired, Mr. Chairman.

Mr. STUPAK. Thank you, Mr. Whitfield. Mr. Walden for questions please.

Mr. WALDEN. Thank you, Mr. Chairman.

Mr. Chairman, one question for you before I ask the witnesses. Did the FDA not want to testify at this hearing, or were they invited or they refused? I know we have had problems in the past, sometimes, getting them here.

Mr. STUPAK. It was decided not to have them at this hearing.

Mr. WALDEN. OK, I hope at a future hearing they are here, because I think it would be good to pose some of these questions to them, and I am disappointed we are not going to have that chance.

Dr. Crosse, let me go to you then. As you mentioned in footnote 2 in your written testimony, the FDA Amendments Act of 2007 gave this new authority to the FDA. The act authorized the FDA to require submission of any draft TV ad for review up to 45 days before it is scheduled to be aired. It gave the FDA the power to impose civil money penalties if statements and drug ads are false or misleading. Is that adequate authority for the FDA?

Ms. CROSSE. I think we don't know yet. These new authorities have not yet been implemented by FDA, and I think it is too soon to see how that will play out. The civil monetary penalties would be a step, in general, beyond what they have been doing with untitled letters and warning letters, the kind of regulatory actions they have been taking. Since in 2007, they only issued two such enforcement letters, I think we are talking about a potentially very small number of actions that would ever arise to the level of civil monetary penalties because in general——

Mr. WALDEN. Is that because most ads aren't false or misleading?

Ms. CROSSE. I can't speak to how many ads have false or misleading content. FDA has not identified that many ads that rose to the level of taking regulatory action, and when they have, the companies have in general been responsive to pull those ads.

Mr. WALDEN. Are you aware of any ads or any companies that have refused to pull an ad?

Ms. CROSSE. I am not aware of any, no, and the increasing number of companies had already voluntarily been submitting broadcast television ads to FDA for advisory opinions prior to broadcast. This new authority will allow FDA to call for companies to do that across the board for the television ads, not the other materials which comprise the bulk of the DTC advertising.

Mr. WALDEN. Let me ask you this question. We have dealt in this oversight subcommittee before on some of the products that are not regulated by the FDA but claim incredible benefit for their usage, and the FDA has really no regulatory authority. I am talking about supplements here. Does the FDA have any authority regarding those advertisements and claims?

Ms. CROSSE. They can take action to ask the companies for support, but they do not have the same authority in this area as they do in the area of prescription drugs and in fact the Federal Trade Commission has been the primary actor in regulating advertising by dietary supplements.

Mr. WALDEN. I know some of the discussion my colleagues were having about the family hour and some of these ads that run, we were having a little chat back here about trying to explain to a teenager about a lot of things, whether it is a Victoria's Secret ad, or feminine products, or some of the supplements that claim incredible, well, you know what I mean. And none of those would really fall under this issue either. And I think we have to be careful in this country to go down a slippery slope when the court has clearly said there is a right to commercial speech for a legal product. Correct? Hasn't the Supreme Court ruled that on commercial speech in this area?

Ms. CROSSE. I am not qualified to speak to that for the direct-to-consumer advertising of prescription drugs, but that certainly is the concern that has been raised about controlling——

Mr. WALDEN. I thought there was a court decision that validated. There certainly have been court decisions that have overturned prohibitions on some liquor advertising. It seems to me that there has to be an overriding public interest issue here, and I am not sure I see it. I hear a lot from my constituents, but the physicians who hate getting this rush of people coming in saying what about this drug. I understand that, and given their time commitments to each patient, that has got to be difficult to manage, but I have always been a believer that more information is better than less, and more freedom of disclosure of information is better than a government censor of information, and that an open and free marketplace, when we are advertising legal drugs that have been approved, I may not like all of those ads, but I guess I have just a little different philosophy about it. Dr. Nielsen, do you have a comment?

Dr. NIELSEN. I do. I think we would absolutely agree with you, and that is why we have been very careful to say that ads that are educational can in fact be beneficial. You will hear things on television and on the radio like know your numbers. That could refer to your blood pressure. It could refer to your cholesterol. That is very helpful. That is important. Patients do need that kind of information. That is really not the concern. It is some of what you heard earlier, although we didn't have the sophistication of the glittery bee wings, which I find very interesting. The risks and benefits, one has to be very careful, because frankly, the educational mission we would support. The marketing we would ask to be fair and balanced.

Mr. WALDEN. All right, and I know my time is expired. I appreciate the testimony of all of our witnesses today. Thank you very much.

Mr. STUPAK. We will go another round of questions if anyone has any more questions. Dr. Nielsen, you indicated the AMA would like the ads to be evidence-based reviewed.

Dr. NIELSEN. We want the ads claiming benefits to be evidence-based and related to what has been presented to the FDA for the indications for which they were approved, yes.

Mr. STUPAK. So evidence-based review would, in a way, work like Dr. Day did, like not speed up the words, not put them at the end where you lose meaning, not to put glitter in bee wings or anything else to distract you, correct?

Dr. NIELSEN. And I think that the study that was referred to earlier that the FDA is proposing to do will look at just that.

Mr. STUPAK. OK, you also mentioned a moratorium so we know the side effects. Could you explain that?

Dr. NIELSEN. It was not quite that. It was when a new product comes to the market, if it is significantly different, then hopefully the FDA would have the authority to negotiate with the manufacturer for a moratorium on DTCA for a period of time to be sure that the information is adequately communicated to physicians first who have to prescribe that drug.

Mr. STUPAK. Well, like the Vytorin. They say in that ad there are two ways you get cholesterol, which is educational, which is good, and it claimed that the drug could address both of those ways, which it did not. So in that instance, because Vytorin was something new, would that be the type of drug you would like to say, well, let's wait a little bit and make sure it works before we put it out advertising it.

Dr. NIELSEN. No, now you are talking about something different. What that ad calls to mind is the issue of emerging science. As the science emerges, that the combination is no more effective than a lesser cost——

Mr. STUPAK. Sure, Zocor.

Dr. NIELSEN. And if that data were in fact suppressed while marketing was going on, that is of grave concern and should be a concern to the country.

Mr. STUPAK. So emerging science should not even be advertised until it is at least proven science.

Dr. NIELSEN. Emerging science, it is really important to recognize the imbalance between what emerges from the scientific literature and the vast resources committed to direct-to-consumer advertising, and we value our colleagues who are in the pharmaceutical industry. We ask them merely to be ethical and fair and when new science emerges to take that into consideration with a fair and balanced ad or pull the ad.

Mr. STUPAK. OK, and let me ask this question to either one of you if you would care to answer. I will take Vytorin, a new drug. It is expensive. I don't have the numbers. It was $8 or $9 a tablet or something. It was quite a bit, and Zocor is 5 cents. Has anyone ever done a study like that only the most expensive drugs are the ones being advertised as opposed to Zocor is just as good as Vytorin, but you don't see it on TV anymore because the patent is

expired? Has anyone ever done that? Are the drugs we are seeing on the TV the expensive ones in those areas? Has Kaiser done that? GAO? AMA?

Dr. NIELSEN. It is very clear that it is the drugs under patent that are being advertised.

Mr. STUPAK. The most expensive drugs then? You don't know or you are not in the position to say?

Dr. NIELSEN. Well, we think we all know the answer to that.

Mr. STUPAK. Yes, I think we all do. All right. Let me ask this. Dr. Crosse, we talked about the chief counsel office and there is a change in policy. Was there a problem before that we had to change the policy so now it takes us so long, like 6 months, to get a letter out to a drug company on advertising? Was there a problem that they highlighted that they said here is why it is going to Chief Counsel so it slows the process down to make sure we do it right? Were there problems?

Ms. CROSSE. It is not clear that there was a problem. The stated purpose for the policy change was to ensure the legal supportability of the letters that were being issued. The letters that had previously been issued had not been challenged, however, on the basis of their legality, so it is not clear that there was a direct link to that. Having said that, we don't object to them wanting to ensure the supportability of the letters they issue. It is the time it has taken, and they committed to issuing those much more quickly in 2002. They said they were putting in place a process to do reviews within 15 days and ensure that letters were issued within 45 days, but every single year, it has continued to lengthen until 2007, and it is now over 6 months to do the review of these, and some of these have had over 30 iterations internally at FDA before a letter has been issued.

Mr. STUPAK. My friend Mr. Shimkus pointed out that we have increased money for the FDA to review these ads. Even with more people there, you may do other things. You may try to streamline it, but as long as we have this bottleneck at the Office of Chief Counsel, it is not going to expedite FDA review of an ad or enforcement action.

Ms. CROSSE. Certainly, we point to that as marking a change that has greatly reduced the number of regulatory actions FDA has taken in this area.

Mr. STUPAK. My time has expired. Anyone else for questions? Mr. Shimkus.

Mr. SHIMKUS. Yes, just real quick, Mr. Chairman. Dr. Nielsen, when a prescription is written, does the doctor list the side effects on the prescription itself?

Dr. NIELSEN. No, sir. That is normally on what the pharmacist will hand to the patient.

Mr. SHIMKUS. Correct. I am just asking the question.

Dr. NIELSEN. But there is a discussion——

Mr. SHIMKUS. See, I really trust my doctor, but we have bad actors in every organization that disappoint us. But I give the physicians a lot more credit than I think you are doing today by them being able to stand up and say I don't care what you are saying. You are my patient. This is not right for you. And I believe that they are strong enough in fortitude and backbone, and I would

trust a doctor over an ad any day of the week because we all know ads are there to sell you things. I mean Cocoa Puffs. You name it. Americans know that because we have free, over-the-air TV, you have to support that through advertising revenue, and advertising is there to sell you things. So I think that is part of our frustration. We love our doctors. They are true professionals, and I just think they are tougher than what is being said here today, and I trust them to be able to stand up against a large pharmaceutical company that may be advertising something that is not in their patients' best interest.

Let me ask you another question. We are going to talk about specific ads in the next panel. Of the three drugs that we are going to be addressing, are all three of them not in compliance based upon evidence? Is there a problem with the evidence behind the claim?

Dr. NIELSEN. I can't comment on those three ads specifically, but I really do need to comment because if I implied in any way that physicians are not acting ethically and they are caving to demands, I really have not conveyed what——

Mr. SHIMKUS. I am just trying to stand up for my doc who I know.

Dr. NIELSEN. I am here to stand up for the hundreds of thousands of educated, ethical, dedicated, and hardworking physicians, but it is true that patients have left physicians because they would not bend to those kinds of marketing pressures.

Mr. SHIMKUS. So then they are going to get the drug from a doc who is not ethical.

Dr. NIELSEN. They will find someone who will prescribe the drug. There are studies to show that. But indeed, doctors work very hard to try to do the right thing for their patients.

Mr. SHIMKUS. That is all I have, Mr. Chairman.

Mr. STUPAK. Mr. Whitfield?

Mr. WHITFIELD. Just one other question, Mr. Chairman, thank you.

Dr. Brodie, I know you have conducted some polling about where patients get information about prescription drugs. Where do direct-to-consumer ads rank for prescription drugs. Would you go through that briefly?

Ms. BRODIE. In the January survey that I talked about before, we asked people to rank sources of information, about how much they information they get, and as we just heard, doctors are right at the top. Seventy-two percent say they get a lot of information about prescription drugs from their doctor. Pharmacists ranked second. Information about the product in the prescription-drug package ranks third. Forty-three percent say they get a lot of that. Twenty-two percent say they get a lot from government agencies like the FDA, families and friends, the Internet, and then at the bottom of the list is ads for prescription drugs in terms of where people say they are getting the most information from.

Mr. WHITFIELD. OK, I yield back the balance of my time.

Mr. STUPAK. Mr. Ferguson for questions?

Just one question. Your survey showed, and you went back and compared it with a survey the Kaiser Foundation did, I believe, back in 1997, people trusted the ads to be accurate more, did they

not, than they do in your survey here in 2005? It was almost like a doubling they lost confidence in these ads.

Ms. BRODIE. Yes, in 1997, I think, 33 percent said they trusted them most of the time, and that was down to 18 percent now, that they could trust what the drug companies had to say in their advertisements most of the time, so that has fallen from 33 percent in 1997 down to 18 percent now. I think that is reflective of the changes that we have seen in DTC advertising. In 1997, they were very new. It was something that were just sort of getting exposed to, and now they are ubiquitous, and now, I think, are assessing the ads more like they are any ad in that they are not new anymore. They are just an advertisement like any other product or service.

Mr. STUPAK. Dr. Nielsen, the AMA is concerned, just in summation in a way, about doctors appearing in ads because of trustworthiness. They have to disclose if they have a fee, and they should have because they are considered experts in these areas. Is that what you are trying to say? I didn't think you were dumping on doctors.

Dr. NIELSEN. Yes, sir. We think doctors should relate to their patients, and they should not be, frankly, hired hucksters for a drug company. And I hate to use that perjorative term, but when one appears in an ad, it implies a credulity that we think is not seemly, and so we strongly discourage it. If they do appear, then we strongly insist that there must be a disclaimer.

Mr. STUPAK. In the Lipitor ad, I want to go back to this just one more time. Dr. Jarvik wasn't licensed to prescribe the medicine. Underneath your rules, he would be considered a doctor, and therefore, underneath your guidelines, he should have disclosed he was a paid consultant. Was that one of the problems with this ad?

Dr. NIELSEN. Well, that would meet our guidelines, yes. You know, I think most Americans know when a celebrity appears in an ad that they probably are compensated for that, but we think with a physician that they should be clear about that.

Mr. STUPAK. With Dr. Jarvik's status, went to medical school, but is not allowed to write a prescription because he is not licensed, would he have had to follow the AMA guidelines? He is not a member, right?

Dr. NIELSEN. No, he is not.

Mr. STUPAK. So there is no requirement on him?

Dr. NIELSEN. We have no enforcement arm, but these are what we strongly recommend.

Mr. STUPAK. OK, anything further? It has been a good panel. We could go on and on, but I think we are going to dismiss you. Thank you all very much for your testimony today.

I would now like to call up our third panel of witnesses and invite them to come forward. On our third panel, we have Mr. James Sage, who is the Senior Director and Team Leader for Lipitor at Pfizer; Mr. Deepak Khanna, who is the Senior Vice President and General Manager of Merck and Schering-Plough Pharmaceuticals; Ms. Kim J. Taylor, who is President of Ortho Biotech, a wholly-owned subsidiary of Johnson & Johnson.

It is the policy of this subcommittee to take all testimony under oath. Please be advised each of you have the right under the rules

of the House to be advised by counsel during your testimony. Do any of you wish to be represented by counsel?

Ms. TAYLOR. I am here with our company's outside counsel, Mr. Lenny Brewer.

Mr. STUPAK. OK, you may consult with him, but he cannot testify, so if you want to consult with him if a question is asked to you, you have a right to do so.

Ms. TAYLOR. Thank you very much.

[Witnesses sworn]

Mr. STUPAK. We will begin with your five-minute opening statement, and we will start from my left. Mr. Sage, would you like to begin, please?

STATEMENT OF JAMES SAGE, SENIOR DIRECTOR/TEAM LEADER, LIPITOR, PFIZER, INC.

Mr. SAGE. Good afternoon, Mr. Chairman, Ranking Member Shimkus and members of the subcommittee. My name is Jim Sage, and I am the senior director and Lipitor team leader for Pfizer, which means that I am responsible for the marketing practices for Lipitor in the U.S. On behalf of Pfizer, I want to thank you for the opportunity to briefly address a few key issues relating to Pfizer's television advertisements for Lipitor, including Pfizer's use of direct-to-consumer advertising, the value of Lipitor, and Dr. Jarvik's role as a spokesperson.

Regarding direct-to-consumer television advertising, Pfizer is committed to responsible advertising that anticipates and addresses the needs of patients and physicians. Pfizer developed safe and effective medicines to prevent and treat some of the world's most serious illnesses. In 2007, we invest $7.6 billion in research and development, and we use DTC to increase awareness of our products, to educate consumers about the conditions that they treat, and to increase patient and physician discussion about those conditions.

Unlike most other industries, pharmaceutical companies cannot sell their products directly to the people who use them. Instead our products must be prescribed by physicians. As a result, the prescribing doctor's role is indispensable when considering the DTC issue. DTC ads encourage an active partnership between patients and their doctors. Millions of Americans suffer from treatable medical conditions that remain undiagnosed, untreated, or under-treated.

This is certainly the case with high cholesterol, only half of those who have this condition have been diagnosed, and of those who have been diagnosed, only half have received treated. Elevated LDL cholesterol is one of the most common risk factors for cardiovascular disease. Heart disease and stroke continue to be a leading cause of death and disability in the United States. Statins, including Lipitor, have played an important role in addressing the risk of heart disease when diet and exercise alone are not enough.

Lipitor itself has been studied for approximately 15 years, in over 400 clinical trials, in over 80,000 patients. Lipitor was in research and development for nearly a decade before coming to market. Our commitment to research did not stop there but continued with several landmark trials. These trials helped form the basis for the current understanding of cardiovascular risk and for updated cardio-

vascular disease-prevention guidelines. In fact, six of these trials have been cited by independent guideline bodies as impacting current standards of care.

What we learned from this research is that when diet and exercise alone are not enough, Lipitor is a safe and effective medicine to reduce LDL cholesterol by 39 to 60 percent and has significantly reduced the risk of heart attack and stroke in a broad range of patients with common risk factors, including hypertension, diabetes, and preexisting heart disease.

Now, let us turn from the science that has proven Lipitor's safety and effectiveness to our company's television advertising campaign for Lipitor featuring Dr. Jarvik. Pfizer asked Dr. Jarvik to appear in Lipitor advertisements because he is recognized for his work related to the human heart. Dr. Jarvik honestly and sincerely embraced our heart health campaign. He and Pfizer believed that the ad were an effective way to deliver an important preventative health message to a large number of patients to encourage them to reduce the risk of heart disease through diet and exercise, was well as through consultation with their doctors about the importance of managing their cholesterol.

Dr. Jarvik received his MD degree from the University of Utah College on Medicine in 1976. Although not a practicing physician, he has devoted his entire career to medical science related to the human heart. He has invented medical devices to help patients with advanced heart disease, and he has collaborated with other physicians and scientist on these activities. As Dr. Jarvik has said publicly, he has the training, experience, and medical knowledge to understand the conclusions of the extensive clinical trials that have been conducted to support the safety and effectiveness of Lipitor. Both Pfizer and Dr. Jarvik are confident that the statements included in these ads fairly represent the scientific data of Lipitor.

Some have asked why Pfizer decided to stop using Dr. Jarvik in our advertisements. We chose Dr. Jarvik to participate in these ads because he is nationally prominent expert, with the knowledge and experience to speak intelligently and sincerely about the benefits of Lipitor. Unfortunately, the way that Dr Jarvik was presented in these ads has created misimpressions and distractions from our primary message which was to encourage patients and physicians to discuss the leading cause of death in the world: cardiovascular disease.

Going forward, we are committed to ensuring there is greater clarity in our advertising regarding the presentation of spokespeople. In summary, Pfizer believes it is important to continue to educate consumers about the risks of elevated cholesterol and the value that Lipitor provides as a potential treatment option. We believe that DTC ads are an effective way to accomplish this objective. Thank you, and I look forward to any questions that you may have.

[The prepared statement of Mr. Sage follows:]

Testimony before the House Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

Statement of
James T. Sage
Senior Director/Team Leader, Lipitor®
Pfizer Inc

May 8, 2008

Good morning Mr. Chairman, Ranking Member Shimkus and Members of the Subcommittee.

My name is Jim Sage, and I am the Senior Director and Lipitor Team Leader for Pfizer, which means that I am responsible for the U.S.-based marketing activities for Lipitor® (atorvastatin calcium) ("*Lipitor*"). Pfizer is the world's largest research-based biomedical and pharmaceutical company. Our people work to discover, develop, manufacture and deliver quality, safe and effective prescription medicines to patients. We have a leading portfolio of medicines that prevent, treat and cure diseases across a broad range of therapeutic areas and that are used to improve the health and lives of millions of Americans.

On behalf of Pfizer, I want to thank you for the opportunity to briefly address a few key issues relating to Pfizer's television commercials for *Lipitor*, including:

- Pfizer's use of direct-to-consumer advertising;
- the value of *Lipitor*;
- Dr. Robert Jarvik's role as spokesperson.

Regarding direct-to-consumer television advertising, Pfizer is committed to responsible advertising that anticipates and addresses the needs of patients and doctors. Pfizer develops safe and effective medicines to prevent and treat the world's most serious

diseases. In 2007, we invested $7.6 billion in research and development. We use DTC to increase awareness of our products, to educate consumers about the conditions that they treat and to increase patient and physician discussion about those conditions.

Unlike most other industries, pharmaceutical companies cannot sell products directly to the people who use them. Instead, these products must be prescribed by physicians. As a result, the prescribing doctor's role is indispensable when considering the DTC issue.

Pfizer believes in the importance of DTC advertising in helping to address critical healthcare needs in this country. We know from research that consumers need and want healthcare information to make educated decisions. However, many consumers face barriers to proper diagnosis and treatment, including lack of information, denial, embarrassment, stigma, low health literacy, coverage, safety concerns and lack of urgency. There is substantial evidence that DTC advertising educates consumers and motivates them to: seek additional information about their medical condition and corresponding treatment options; consult their physicians for diagnosis and appropriate treatment; and follow the treatment plans directed by their physicians.

DTC ads encourage an active partnership between patients and their doctors. Millions of Americans suffer from treatable medical conditions that remain undiagnosed, untreated or under-treated. This is certainly the case with high cholesterol, as only half of those with this condition have been diagnosed and only half of those diagnosed receive treatment. Elevated LDL cholesterol is one of the most common risk factors for cardiovascular disease. Heart disease and stroke continue to be leading causes of death and disability in the United States. Statins, including *Lipitor*, have played an important

role in addressing the risks of heart disease when diet and exercise alone are not enough. 2005 data from the United States Centers for Disease and Control show that since 1999, deaths from cardiovascular heart disease have dropped by more than 25%, and deaths from stroke have fallen by 24%. A number of factors have contributed to this, including advancements in available treatment options for major risk factors – including cholesterol reduction.

Lipitor itself has been studied for about 15 years in more than 400 clinical trials, including more than 80,000 patients. *Lipitor* was in research and development for nearly a decade before coming to market. Our commitment to research did not stop there but continued with several landmark trials published in leading peer-reviewed medical journals, including the *New England Journal of Medicine*, *the Lancet*, the *Journal of the American Medical Association*, and the *Journal of the American College of Cardiology*. These trials helped form the basis for current understanding of cardiovascular risk and for updated cardiovascular disease prevention guidelines. In fact, six of these trials have since been cited by independent guideline bodies as impacting current standards of care.

What we've learned from this research is that, when diet and exercise alone are not enough, *Lipitor* is a safe and effective medicine to:

- Significantly lower LDL by 39-60%; and
- Significantly reduce the risk of heart attack and stroke in a broad range of patients with common risk factors like hypertension, diabetes or history of heart disease

Now, let's turn from the science that has proven *Lipitor*'s safety and effectiveness to our company's television advertising campaign for *Lipitor* featuring Dr. Jarvik.

Pfizer asked Dr. Jarvik to appear in *Lipitor* advertisements because he is recognized for his work related to the human heart. Dr. Jarvik honestly and sincerely embraced our heart health campaign. He and Pfizer believe the ads were an effective way to deliver an important preventive health message to a large number of people by encouraging them to reduce the risk of heart disease through diet and exercise as well as consultation with their doctors about the importance of managing cholesterol.

Dr. Jarvik received his M.D. degree from the University of Utah College of Medicine in 1976. Although not a practicing physician, he has devoted his entire career to medical science related to the human heart. He has invented medical devices to help patients with advanced heart disease, and has collaborated with other physicians and scientists on these activities. As Dr. Jarvik has said publicly, he has "the training, experience, and medical knowledge to understand the conclusions of the extensive clinical trials that have been conducted to study the safety and effectiveness of *Lipitor*." Both Pfizer and Dr. Jarvik are confident that the statements included in the ads fairly represent the scientific data about *Lipitor*.

An important objective of the Jarvik advertising campaign for *Lipitor* was to highlight the importance of diet and exercise in reducing cardiovascular risk. When diet and exercise are not enough, adding medication such as *Lipitor* may be an important consideration for doctors and patients to discuss.

Some have asked why Pfizer decided to stop using Dr. Jarvik in our advertising. We chose Dr. Jarvik to participate in these ads because he is a nationally prominent expert with the knowledge and experience to speak intelligently and sincerely about the benefits of *Lipitor*. Unfortunately, the way Dr. Jarvik was presented in these ads has

created misimpressions and distractions from our goal of encouraging patient and physician dialogue about the leading cause of death in the world: cardiovascular disease. Going forward, we are committed to ensuring there is greater clarity in our advertising regarding the presentation of spokespeople.

In summary, Pfizer believes that it's important to educate consumers about the risks associated with elevated cholesterol and the value of *Lipitor* as a potential treatment option. We believe that DTC ads are an effective way of accomplishing that objective.

Thank you, I look forward to answering any questions you may have.

Mr. STUPAK. Thank you, doctor. Mr. Khanna, your opening statement please, sir. And for all of the witnesses, if you have a longer opening statement, we will be happy to include it in the record. OK, Mr. Khanna.

STATEMENT OF DEEPAK KHANNA, SENIOR VICE PRESIDENT AND GENERAL MANAGER, MERCK/SCHERING-PLOUGH PHARMACEUTICALS

Mr. KHANNA. Mr. Chairman, Ranking Member Shimkus and members of the committee, I am Deepak Khanna, senior vice president and general manager of Merck/Schering-Plough Pharmaceuticals. Like many Americans, I try to control my cholesterol through diet and exercise. Merck and Schering Plough formed Merck/Schering-Plough Pharmaceuticals in 2000 to make available important treatment choices for patients, who unlike me, cannot maintain a healthy cholesterol level through diet and exercise alone.

As early as 1961, scientists identified elevated levels of cholesterols as among the risk factors for coronary heart disease, the leading killer of Americans. Lowering LDL cholesterol through diet, exercise, and if necessary, pharmaceutical treatment is the cornerstone of heart disease prevention. Mr. Chairman, despite our advances in the understanding of the role of high cholesterol in heart disease in and in the development of effective treatment, the toll of heart disease remains too high, and the level of understanding and treatment remain too low.

Approximately 46 million adults in the U.S. have been diagnosed with high cholesterol and might benefit from pharmaceutical treatment. However, just 14.5 million adults are currently being treated with a cholesterol-lowering medication. Of those treated, more than 4 million, or nearly one-third, are not attaining the desired cholesterol goals established by the NIH's National Cholesterol Education program. The result is unnecessary disease and suffering.

It is against this backdrop that Merck/Schering-Plough Pharmaceuticals approached the decision to create and broadcast advertisements for Vytorin, which is combination of two medicines, Zetia, which limits the absorption of cholesterol from food, and simvastatin, a statin medicine that moderates the body's inherited, natural production of cholesterol.

High cholesterol alone has no symptoms. Advertising can be especially helpful in informing people about the need to address this important condition as well as reminding them to fill their prescriptions and take their medicines as directed by their physician. As we developed our advertising, we learned that the vast majority of people understood the role of diet and exercise in cholesterol control but did not appreciate the genetic causes. This leads to them disproportionately blaming themselves for a condition that is often inherited. The advertising that Merck/Schering-Plough broadcast from September 2004 until January of this year used a unique, memorable, effective approach to educate about the importance of lowering cholesterol, the two sources of cholesterol, the importance of diet, and the additional LDL lowering that can come from drug therapy when a healthy diet is not enough.

Our food and family advertisements were entertaining. This approach kept consumers engaged while we delivered a serious educational message, and our consumer research has consistently shown that the information about the two sources of cholesterol is getting through. We commissioned a Harris survey that found that prior to our advertising, just 16 percent of people were aware that there two sources of cholesterol. In the year following our advertising, we found a full 54 percent of people now understood this. We also learned that our advertising had helped relieved the guild people often carry when they are unable to control their high cholesterol with diet and exercise and encouraged them to have discussions with their physicians about additional options for controlling their cholesterol.

In developing the advertising campaign, we sought advice from the Food and Drug Administration on the proposed content of our advertisements and revised our advertisements in response to those comments. These advertisements only made claims that were supported by research that were evaluated by the FDA and that were consistent with our FDA-approved labeling. Merck/Schering-Plough Pharmaceuticals suspended our Vytorin food and family broadcast advertising in January. We took this action in anticipation of the confusion that could be created by our release of the results of the enhanced trial.

Mr. Chairman, the enhanced trial was a relatively small study of a unique patient population that was genetically predisposed to very high levels of LDL cholesterol. Enhanced compared the impact of Vytorin versus simvastatin on a surrogate market fro heart disease, reduction in the thickness of the carotid arterial wall. While there was no difference on this measurement between the two treatments, Vytorin did demonstrate superior LDL lowering compared to simvastatin.

Merck/Schering-Plough Pharmaceuticals stands behind the benefits of Vytorin in lowering LDL cholesterol. We will continue to responsibly inform patients and prescribers about LDL cholesterol, the importance of diet and exercise, and Vytorin. As we move forward, we will continue to consult with physicians, patients, and the FDA to ensure that the information we provide will continue to educate and motivate patients to improve their health. I appreciate the opportunity to appear before you and welcome your questions.

[The prepared statement of Mr. Khanna follows:]



MERCK / Schering-Plough Pharmaceuticals

Summary of Testimony of
Deepak Khanna, Senior Vice President and General Manager,
Merck/Schering-Plough Pharmaceuticals
before the Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
United States House of Representatives

May 8, 2008

As early as 1961, scientists identified elevated levels of cholesterol as among the risk factors for coronary heart disease, the leading killer of Americans. Lowering cholesterol – and specifically LDL cholesterol – through diet, exercise, and, if necessary, pharmaceutical treatment is the cornerstone of heart disease prevention.

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Vytorin is a combination of two medicines: Zetia, which limits the absorption of cholesterol from food, and simvastatin, a statin medicine that moderates the body's inherited natural production of cholesterol.

The Vytorin advertising that Merck/Schering-Plough Pharmaceuticals broadcast from September of 2004 until January of this year used an effective approach to educate patients about the importance of lowering cholesterol, the two sources of cholesterol, the importance of diet and the additional LDL lowering that can come from drug therapy when a healthy diet is not enough.

These advertisements only made claims that are supported by research, that were evaluated by the Food and Drug Administration, and that were consistent with our FDA-approved labeling. In developing the advertising campaign, we sought advice from the FDA on the proposed content of our advertisements and revised them in response to those comments.

Merck/Schering-Plough Pharmaceuticals stands behind the benefits of Vytorin in lowering LDL cholesterol. We will continue to responsibly inform patients and prescribers about LDL cholesterol, the importance of diet and exercise, and Vytorin. As we move forward, we will continue to consult with physicians, patients and the FDA to ensure that the information we provide will continue to educate and motivate patients to improve their health.



MERCK / Schering-Plough Pharmaceuticals

Testimony of
Deepak Khanna, Senior Vice President and General Manager,
Merck/Schering-Plough Pharmaceuticals
before the Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
United States House of Representatives

May 8, 2008

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Mr. Chairman, despite our advances in the understanding of the role of high cholesterol in heart disease and in the development of effective treatments, the toll of heart disease remains too high and the level of understanding and treatment remain too low.

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cholesterol goals established by the NIH's National Cholesterol Education Program. The result is unnecessary disease and suffering.

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High cholesterol alone has no symptoms. Advertising can be especially helpful in informing people about the need to address this important condition, as well as reminding them to fill their prescriptions and take their medicines as directed by their physician. As we developed our advertising, we learned that the vast majority of people understood the role of diet and exercise in cholesterol control, but did not appreciate the genetic causes. This leads to their disproportionately blaming themselves for a condition that is often inherited.

The advertising that Merck/Schering-Plough Pharmaceuticals broadcast from September of 2004 until January of this year used a unique, memorable, effective approach to educate about the importance of lowering cholesterol, the two sources of cholesterol, the importance of diet and the additional LDL lowering that can come from drug therapy when a healthy diet is not enough.

Our food and family advertisements were entertaining. This approach kept consumers engaged while we delivered a serious educational message. And our consumer research has consistently shown that the information about the two sources of cholesterol is getting through.



MERCK / Schering-Plough Pharmaceuticals

We commissioned a Harris survey that found that, prior to our advertising, just 16 percent of people were aware that there were two sources of high cholesterol. In the year following our advertising, we found that a full 54 percent of people now understood this. We also learned that our advertising had helped relieve the guilt people often carry when they are unable to control their high cholesterol with diet and exercise and encouraged them to have discussions with their physicians about additional options for controlling their cholesterol.

In developing the advertising campaign, we sought advice from the Food and Drug Administration on the proposed content of our advertisements and revised our advertisements in response to those comments. These advertisements only made claims that are supported by research, that were evaluated by the FDA, and that were consistent with our FDA-approved labeling.

Merck/Schering-Plough Pharmaceuticals suspended our Vytorin food and family broadcast advertising in January. We took this action in anticipation of the confusion that could be created by our release of the results of the ENHANCE trial.

Mr. Chairman, the ENHANCE trial was a relatively small study of a unique patient population that was genetically predisposed to very high levels of LDL cholesterol. ENHANCE compared the impact of Vytorin versus simvastatin on a surrogate marker for heart disease – reduction in the thickness of carotid arterial wall. While there was no difference on this measurement between the two treatments, Vytorin did demonstrate superior LDL-lowering compared to simvastatin.



MERCK / Schering-Plough Pharmaceuticals

Merck/Schering-Plough Pharmaceuticals stands behind the benefits of Vytorin in lowering LDL cholesterol. We will continue to responsibly inform patients and prescribers about LDL cholesterol, the importance of diet and exercise, and Vytorin. As we move forward, we will continue to consult with physicians, patients and the FDA to ensure that the information we provide will continue to educate and motivate patients to improve their health.

I appreciate the opportunity to appear before you and welcome your questions.

Mr. STUPAK. Thank you. Ms. Taylor, your opening statement please.

STATEMENT OF KIM TAYLOR, PRESIDENT, ORTHO BIOTECH, INC.

Ms. TAYLOR. Chairman Stupak, Ranking Member Shimkus, and members the subcommittee, good afternoon. I am Kim Taylor, the president of Ortho Biotech. I am pleased to be here today to speak with you about direct-to-consumer advertising, and in particular, the broadcast television advertisements of Ortho Biotech's medicine Procrit, which the company stopped airing 3 years ago. Because the subcommittee expressed interest in our history of Procrit television advertisements, which focused on the treatment of anemia associated with cancer chemotherapy, I will focus my testimony on this indication.

When the FDA approved Procrit for the treatment of chemotherapy-induced anemia, it premised the approval on the ability of ESAs to treat anemia by increasing a patient's hemoglobin, reducing the likelihood that a chemotherapy patient would require a transfusion of red blood cells and reduced the amount of blood that would be needed in the case of a transfusion. ESAs are very effective at reducing a chemotherapy patient's need for transfusion. As the FDA stated in its March 2008 briefing at the Oncologic Drugs advisory committee review of ESAs, across several studies, approximately 50 percent of anemia patients receiving chemotherapy required transfusions, as compared to approximately 20 to 25 percent of patients who received ESAs concurrently with chemotherapy.

The development of a product that could reduce chemotherapy-related transfusions was important to patients. Before Procrit and other ESAs became available, anemic chemotherapy patients faced the choice of living with anemia and the significant impact on even the most basic activities of daily living, or that could require interrupting chemotherapy treatment, or accepting the discomfort and medical risks associated with multiple transfusions.

I would like to describe for the subcommittee my understanding of the process by which Ortho Biotech undertook direct-to-consumer advertisements for Procrit. I should note at the outset that I was not employed with Ortho Biotech at the time, so I have no firsthand knowledge of these events. I have, however, endeavored over the past several weeks to gather and become familiar with the history of Ortho Biotech's Procrit advertisements.

During the middle 1990s, cancer doctors began to have a greater awareness of a practice that is generally called supportive care. Consistent with an increased focus on supportive care, researchers investigated the use of Procrit to address chemotherapy patients' anemia and decrease the need for transfusion. Studies validated the use of Procrit in this way. At the same time, any patients with chemotherapy-include anemia were under-diagnosed for this condition, and some patients were even unaware that anemia could cause fatigue and tiredness. Others were not candid about their fatigue for fear that their doctor could possibly interrupt their life-saving chemotherapy treatment.

In this environment, Ortho Biotech undertook a comprehensive educational campaign that included programs of outreach to pa-

tients, patient educational campaigns, and direct-to-consumer advertising. Ortho Biotech believed that direct-to-consumer advertising as one part of a comprehensive educational effort was an effective way to raise awareness about chemotherapy-induced anemia. The Procrit broadcast advertisements ran from 1998 to 2005. All of the ads communicated the same general theme: chemotherapy-induced anemia can cause fatigue and weakness, and Procrit may alleviate those symptoms by addressing the chemotherapy-induced anemia. A central message of each and every advertisement was to encourage the patient to talk to his or her doctor about the symptoms of anemia. Only through discussing these symptoms with a doctor could the doctor then make the medical determination of whether that patient would benefit from Procrit.

As the committee reviews Ortho Biotech's direct-to-consumer broadcast advertisements for Procrit, I would like to stress four fundamental points. First, the statements in the advertisements regarding the benefits of Procrit were true, responsible, and substantiated by clinical studies, showing that the administration of Procrit led to significant improvements in the symptoms of anemia in chemotherapy patients. Second, the advertisements were consistent with the FDA-approved indication for Procrit, in this case, the treatment of chemotherapy-induced anemia. The advertisements, therefore, discussed the symptoms of chemotherapy-induced anemia, such as fatigue and weakness, and very carefully made clear that Procrit treats chemotherapy-induced anemia or increases red blood cells. Third, the advertisements began 5 years after Procrit was approved for the treatment of chemotherapy-induced anemia, well beyond the current pharmaceutical industry's and Johnson & Johnson's own internal guidelines on the waiting period for direct-to-consumer advertising. And finally, the advertisements were submitted to the FDA, as required by regulations, and Ortho Biotech had extensive and ongoing discussions with appropriate FDA officials about the content of the advertisements.

As the state of the medical knowledge evolved over time, Ortho Biotech has worked closely with the FDA to ensure that new and relevant information was included in the label and raised as appropriate in the advertisements. In 2005, Ortho Biotech ended its Procrit direct-to-consumer broadcast advertising. Ortho Biotech believed that patients suffering from chemotherapy-induced anemia were aware of Procrit as a treatment option to discuss with their physicians and that ESAs were established as within the standard of care for chemotherapy-induced anemia. We have no current plans to resume Procrit direct-to-consumer television advertisements.

Procrit remains an important medicine for its approved indications. Procrit and other ESAs continue to provide significant benefits to patients with chemotherapy-induced anemia, and I would be happy to answer any questions that you have.

[The prepared statement of Ms. Taylor follows:]

STATEMENT OF KIM TAYLOR

Chairman Stupak, Ranking Member Shimkus, and Members of the Subcommittee, good morning. I am Kim Taylor, the President of Ortho Biotech, and I am pleased to be here today to speak with you about direct-to-consumer advertising, and in par-

ticular, the broadcast television advertisements of Ortho Biotech's medicine Procrit*, which the company stopped airing 3 years ago.

Ortho Biotech, a member of the Johnson & Johnson family of companies, is a leading biopharmaceutical company that provides innovative products and services designed to help enhance the lives of individuals with serious chronic illnesses. Ortho Biotech is a leader in the research and treatment of anemia, which is a blood condition identified by a deficiency of hemoglobin sufficient to cause symptoms. Hemoglobin is a component of red blood cells, and its purpose is to transport oxygen from the lungs to all tissues of the body. Symptoms of anemia include weakness and fatigue because the tissues of the body are not getting enough oxygen to function properly.

A class of medicines known as erythropoiesis-stimulating agents (ESAs) can treat anemia because they are biologically similar to the naturally occurring protein erythropoietin, which stimulates red blood cell production. The first ESA approved in the United States was epoetin alfa, the medicine that is marketed by Ortho Biotech under the brand name Procrit.

Ortho Biotech distributes Procrit under an agreement with Amgen, the initial developer of epoetin alfa. Under that agreement, Ortho Biotech distributes the medicine for patients not on dialysis. The FDA granted the first approved indication for the medicine, the treatment of chronic renal failure, in 1989. Since then, the FDA has approved three additional indications: In 1991, it was approved for the treatment of anemia in zidovudine (AZT) therapy in HIV-infected patients. In 1993, the medicine was approved for the treatment of anemia associated with cancer chemotherapy. And in 1996, the FDA approved the medicine for administration before surgery as a means to reduce transfusions.

Because the Subcommittee expressed interest in our history of Procrit television advertisements, which focused on the treatment of anemia associated with cancer chemotherapy, I will focus my testimony on this indication.

When the FDA approved Procrit for the treatment of chemotherapy-induced anemia, it premised the approval on the ability of ESAs to treat anemia by increasing a patient's hemoglobin, reducing the likelihood that a chemotherapy patient would require a transfusion of red blood cells, and reducing the amount of blood that would be needed in the case of transfusion. ESAs are very effective at reducing a chemotherapy patient's need for transfusions. As the FDA stated in its March 2008 briefing for the Oncologic Drugs Advisory Committee review of ESAs, "[a]cross several studies, approximately 50% of anemic patients receiving chemotherapy required transfusions as compared to approximately 20–25% of patients who received ESAs concurrently with chemotherapy."

The development of a product that could reduce chemotherapy-related transfusions was important to patients. Before Procrit and other ESAs became available, anemic chemotherapy patients faced the choice of living with anemia, which could require interrupting chemotherapy treatment, or accepting the discomfort and medical risks associated with transfusions, including HIV, Hepatitis B and C, bacterial infection, and transfusion-related acute lung injury, each of which can be fatal. Avoidable transfusions also burden the blood supply. Because the only source of blood is the voluntary donation by individuals, the blood supply is under constant pressure.

I would like to describe for the Subcommittee my understanding of the process by which Ortho Biotech undertook direct-to-consumer advertisements for Procrit. I should note, at the outset, that I was not employed with Ortho Biotech at the time, so I have no first hand knowledge of these events. I have, however, endeavored over the past several weeks to gather and become familiar with the history of Ortho Biotech's Procrit advertisements.

During the middle 1990s, cancer doctors began to have a greater awareness of a practice that is generally called ″supportive care.″ Supportive care is treatment given to prevent, control, or relieve complications and side effects of an illness or its treatment. Management of chronic cancer pain is perhaps the most well known supportive care measure, and the treatment of chemotherapy-induced anemia is another example. Consistent with an increased focus on supportive care, researchers investigated the use of Procrit to address chemotherapy patients' anemia and decrease the need for transfusions. Studies validated the use of Procrit in this way.

At the same time, many patients with chemotherapy-induced anemia were underdiagnosed for the condition. Some patients were even unaware that anemia could cause fatigue and tiredness. Others were not candid about their fatigue for fear that their doctor could possibly interrupt their lifesaving chemotherapy treatment. Indeed, cancer patients described fatigue as having a significant impact on their daily

* Procrit (epoetin alfa) is a registered trademark of Ortho Biotech Products, L.P.

lives, yet there was low awareness that chemotherapy related fatigue may be caused by anemia and that there were treatments for chemotherapy-induced anemia. In this environment, Ortho Biotech undertook a comprehensive educational campaign that included programs of outreach to doctors, patient educational campaigns, and direct-to-consumer advertising. Ortho Biotech believed that direct-to-consumer advertising, as one part of a broader comprehensive educational effort, was an effective way to raise awareness about chemotherapy-induced anemia.

I should pause here to note that our parent company, Johnson & Johnson, was a key player in the development of industry guidelines for direct-to-consumer advertising. In addition to adhering to the industry-wide guidelines, Johnson & Johnson adopted its own internal guiding principles that are even more rigorous than the industry guidelines. Although the development of the Procrit advertisements preceded these guidelines, the creative development process for the Procrit advertisements was carefully reviewed by Ortho Biotech's Promotional Review Committee. This group is composed of individuals from the legal, regulatory, medical, clinical, and health care compliance departments of the company. Through consultation and review of the activities of the Procrit marketing group, the Promotional Review Committee ensured that the advertisements complied with FDA regulations and were consistent with the approved indications.

Our development of the Procrit ads began with an assessment of the patient audience that would be viewing the ads, including extensive individual interviews with chemotherapy patients. Our goal was to understand the patients, their needs, and the most effective way to reach those who may be suffering from chemotherapy-induced anemia.

The Procrit broadcast advertisements ran from 1998 until 2005. All of the ads communicated the same general theme: chemotherapy-induced anemia can cause fatigue and weakness, and Procrit may alleviate those symptoms by addressing the chemotherapy-induced anemia. A central message of each and every advertisement was to encourage the patient to talk with his or her doctor about the symptoms of anemia. Only through discussing these symptoms with a doctor could the doctor then make the medical determination of whether that patient would benefit from Procrit.

As the Committee reviews Ortho Biotech's direct to consumer broadcast advertisements for Procrit, I would like to stress four fundamental points. First, the statements in the advertisements regarding the benefits of Procrit were true, responsible, and substantiated by scientific studies showing that administration of Procrit led to significant improvements in the symptoms of anemia in chemotherapy patients. Second, the advertisements were consistent with the FDA-approved indication for Procrit—in this case, the treatment of chemotherapy-induced anemia. The advertisements, therefore, discussed the symptoms of chemotherapy-induced anemia - such as fatigue and weakness—and very carefully made clear that Procrit treats chemotherapy-induced anemia or increases red blood cells. Third, the advertisements began five years after Procrit was approved for treatment of chemotherapy-induced anemia, well beyond the pharmaceutical industry's and Johnson & Johnson's own internal guidelines on direct-to-consumer advertising. Fourth, the advertisements were submitted to the FDA as required by regulations, and Ortho Biotech had extensive and ongoing discussions with appropriate FDA officials about the content of the advertisements. As the state of the medical knowledge evolved over time, Ortho Biotech has worked collaboratively with the FDA to ensure that new and relevant information was included in the label and raised as appropriate in the advertisements.

In mid-2005, Ortho Biotech ended its Procrit direct-to-consumer broadcast advertising. Ortho Biotech's decision to conclude the Procrit broadcast advertisements was related in part to the reason that we began the ads in 1998—the awareness in the doctor and patient community about the symptoms and treatment of chemotherapy-induced anemia. By the early 2000s, Ortho Biotech believed that patients suffering from chemotherapy-induced anemia were aware of Procrit as a treatment option to discuss with their physicians, and that ESAs were established as within the standard of care for chemotherapy-induced anemia. Given this heightened awareness and other business considerations, Ortho Biotech concluded that further investment in Procrit direct-to-consumer advertising was no longer warranted. We have no current plans to resume Procrit direct-to-consumer television advertisements.

Procrit remains an important medicine for its approved indications. Procrit and other ESAs continue to provide significant benefits to patients with chemotherapy-induced anemia, particularly when an ESA is the only available means to reduce the need for blood transfusions. Procrit is safe and effective for the treatment of

chemotherapy-induced anemia when it is used in accordance with its FDA-approved prescribing information.

I would be happy to answer any questions that you might have.

Mr. STUPAK. Thank you, and thank you to each of you for being here today. We will probably go a couple of rounds of questions, so let us start with Mr. Sage. Mr. Sage, in that binder right there, I want to go to a couple of exhibits. I am looking at exhibit 10 and exhibit 11, page 8. This is your marketing research, and it is basically a report on the research of having Dr. Jarvik in there. There are a lot of things like, "he is an expert in cardiology. His resume and his background speaks for itself. I cannot conceive a man that would be out there selling a product with that type of background, integrity. I don't think he is doing it for the money. I think he is doing it because he has found something that helps. Jarvik knows the heart. He is not a paid actor, not a fly-by-night." It doesn't really show that people who viewed the Jarvik ads were likely to believe that Dr. Jarvik was not being paid to do the commercials.

Mr. SAGE. So your question was whether or not it was clear that he wasn't being paid?

Mr. STUPAK. Well, it is the perception of the people there, according to your two marketing reports, right?

Mr. SAGE. Just to clarify, these reports are 2 out of 30 reports that we have done with consumers on Lipitor. These reports are qualitative in nature. The one report is a study done with about——

Mr. STUPAK. My question, and I know there are a lot more of those reports, that is why I went to specifically page 8. I was talking about how the people perceived Dr. Jarvik as not being a paid spokesperson, but yet, in fact, he was paid, right?

Mr. SAGE. He was paid. Just to clarify, that is quote from a single physician in a study of 20 physicians.

Mr. STUPAK. You are on exhibit 10 and exhibit 11, right?

Mr. SAGE. Yes, sir.

Mr. STUPAK. All right. Page 11, Pfizer, Mindy Goldberg Association, Lipitor, generic defense, consumer qualitative research, page 8 has all of these individuals' statements on there. That is not a one-pager from some doctor.

Mr. SAGE. Just to clarify, Mr. Chairman, this is a study that was done with an outside vendor.

Mr. STUPAK. For Pfizer.

Mr. SAGE. For Pfizer.

Mr. STUPAK. For you, and the impact that the Jarvik ads were having.

Mr. SAGE. Yes, with——

Mr. STUPAK. And how people were perceiving it. On page 8, there it tells how people are perceiving it, right?

Mr. SAGE. It is one physician's opinion of Dr. Jarvik. It is a study of 20 physicians.

Mr. SHIMKUS. Mr. Chairman, we may be on different—I want to make sure we are on the same—I don't know if we are on the same——

Mr. STUPAK. Exhibit 11. It is about——

Mr. SHIMKUS. They are tabs, so——

Mr. STUPAK. It is about 14 pages, Mindy Goldberg Associates Incorporated, Lipitor generic defense, consumer qualitative research, right?

Mr. SAGE. Yes, we are looking at the same thing, sir.

Mr. STUPAK. OK. So how can you say that is one physician?

Mr. SAGE. Just to clarify, we have done over 30 studies with consumers on Lipitor. The overwhelming——

Mr. STUPAK. Right, I know, but I am asking about this study, about——

Mr. SAGE. Sure, it is one study with 20 physicians. What she is quoting is a quote from one physician of those 20. It is not a projectable——

Mr. STUPAK. So even this one physician, if you believe it is— so you say it is one physician. "He is an expert. He knows the heart. He is not a paid actor and not even a fly-by-night guy." Right. That is what the——

Mr. SAGE. That is what it says, yes, sir.

Mr. STUPAK. OK, and then on the other one, page 10, basically it says the same thing: "I like the Dr. Jarvik ads best of all because in my mind, he is not being paid. He is a real person. He is not a sterile doctor. He is an expert. He invented the artificial heart. He is an expert in cardiology." So——

Mr. SHIMKUS. These are from tab 10 now.

Mr. STUPAK. Right, these are tab 10, right?

Mr. SAGE. I am with you, sir, yes.

Mr. STUPAK. So, and you never disclosed that Dr. Jarvik was paid?

Mr. SAGE. We did not.

Mr. STUPAK. This person might have had a different review or comments for you if he would have known Dr. Jarvik was paid, right?

Mr. SAGE. It is possible, yes, sir.

Mr. STUPAK. And are you aware of the AMA guidelines that if a health professional appears in ads, it is recommended that it be disclosed that they are being paid?

Mr. SAGE. I am, Chairman, yes.

Mr. STUPAK. OK, well, why didn't you do that then?

Mr. SAGE. As I understand, the decision at the time, we consulted what we thought were the appropriate guidelines, which were the Pharma code, our own internal guidelines on DTC, as well as the FDA through pre-clearance. The reason we didn't look at the AMA guidelines is because we didn't consider Dr. Jarvik a prescribing physician.

Mr. STUPAK. But you represented him as a physician, right?

Mr. SAGE. We represented him very clearly as the inventor of the artificial heart, which was disclosed——

Mr. STUPAK. Well that brings me to my next question. Go to exhibit 6, tab 6 there. Dr. Jarvik's own colleagues write that, "Dr. Jarvik is not the inventor of the artificial heart." And they requested that the Lipitor ads be corrected to accurately describe Dr. Jarvik's contribution as one of the designers of the artificial heart. He is not the inventor of the artificial heart. Is that what it says?

Mr. SAGE. That is what it says, yes, sir.

Mr. STUPAK. OK, so if you are not portraying him as a prescribing physician, and he is not the inventor of the artificial heart, then how are you portraying Dr. Jarvik then?

Mr. SAGE. We actually took corrective measures based on this feedback. We clarified the communication. We pointed out that he is the inventor of the Jarvik artificial heart, so this was taken into account, Mr. Chairman.

Mr. STUPAK. All right, let me ask you this one. Exhibit 14 and 15, based on this document, it appears that Pfizer was about to embark upon a Doctors for Lipitor campaign, right?

Mr. SAGE. It was an idea that was under consideration.

Mr. STUPAK. And that was based on the success of the Jarvik campaign, right, exhibit 10 and 11 that we showed you earlier?

Mr. SAGE. It was, in part, influenced by our prior experience, yes, Mr. Chairman.

Mr. STUPAK. And a couple of doctors have agreed to do ads for Lipitor? Dr. Robert Cloner and Dr. Lori Mosca?

Mr. SAGE. At the time, two physicians had expressed some interest. I might point out, though, that this is a campaign that we are not moving forward with.

Mr. STUPAK. Right. Do you think that the use of Dr. Jarvik and the way it was misrepresented in your ads could have alienated health professionals from being willing to participate in direct-to-consumer ads, as Dr. Nielsen sort of testified to in the first panel? Not specific to Lipitor, but if we misrepresent the healthcare professions, they are going to be less likely to appear in ads, and they didn't want that taint, if you will, on the medical profession. Is that fair to say?

Mr. SAGE. I think it is fair to say that no physician wants to taint the medical profession, nor does Pfizer.

Mr. STUPAK. OK, my time is up. I think we will go more than one round. I didn't get to the other witnesses yet.

Mr. Shimkus, questions?

Mr. SHIMKUS. Thank you, Mr. Chairman. A couple questions: in your own particular processes when you are moving to market a drug, do you all have a promotional review committee? Is there a doctor-based review committee on the advertising?

Mr. SAGE. Sure, all of the promotional materials that we develop, whether they are for professionals or consumers, go through an internal review process. It includes review from lawyers, regulatory people, as well as physicians, and then all of those materials are filed with FDA.

Mr. SHIMKUS. Mr. Khanna?

Mr. KHANNA. Sure, yes, we have a very extensive review process that includes not only physicians, people familiar with the regulator process, as well as legal folks, and in addition, these ads are pre-submitted to the FDA.

Mr. SHIMKUS. I am going to get to the FDA in a moment. Ms. Taylor?

Ms. TAYLOR. Yes, we also have a protocol review committee that is comprised of medical, regulatory, legal experts, and so on, and they all review all of the materials prior to them being finished.

Mr. SHIMKUS. And the follow-up question is, these doctors, are they licensed physicians? And I guess a more clarifying question would be in the specialty of the drug.

Mr. SAGE. It depends. You have a mix of physicians on the Lipitor team, some of whom are licensed, some of whom are not, all of whom have spent a lot of time on the Lipitor clinical programs, so they are very familiar with the data.

Mr. SHIMKUS. Mr. Khanna?

Mr. KHANNA. They are licensed, and they are familiar with the data.

Mr. SHIMKUS. And Ms. Taylor?

Ms. TAYLOR. Also, for us they are licensed and board certified.

Mr. SHIMKUS. A follow-up question to all three, are they paid by you all as part of this committee? I would imagine that a stipend would have to be paid just to encourage them to come and spend a day or two to do the review, but I am asking the question because I really don't know.

Mr. SAGE. Congressman, in Pfizer's case these are employees of Pfizer.

Mr. SHIMKUS. Thank you.

Mr. KHANNA. These are employees of Merck/Schering-Plough.

Ms. TAYLOR. And also in the case of Ortho Biotech, they are employees.

Mr. SHIMKUS. OK, in all of the opening statements, we talked about the FDA process. I probably could have talked to the chairman. He is a good friend of mine. And if I would have done a better review, I might have said why don't we have someone from the FDA? We didn't. But the more I hear the testimony, based upon submissions and consultations, in all of these cases, you have done some of that, have you not, Mr. Sage?

Mr. SAGE. Correct. The ad in question and future ads in the Jarvik campaign were submitted to FDA for comments.

Mr. SHIMKUS. And did they return comments?

Mr. SAGE. They did.

Mr. SHIMKUS. Were they anything earth shattering?

Mr. SAGE. All of the FDA comments were taken into consideration.

Mr. SHIMKUS. Did you change anything because of the comments?

Mr. SAGE. We did, sir.

Mr. SHIMKUS. I used to teach high school. I am not going to let you get away with just a yes or no. I need more information. Can you give me an example of something you changed?

Mr. SAGE. Sure. One of the claims that the FDA had a question about or a concern about was an efficacy claim that we made against other LDL-lowering medicines, about our ability to lower cholesterol, and we narrowed that claim to be more precise to existing data.

Mr. SHIMKUS. Mr. Khanna, same line please.

Mr. KHANNA. Yes, we did pre-submit our ads to the FDA. We did receive comments from the FDA, and we did incorporate those comments. A specific example is they asked us to strengthen the importance of diet in our ads and we did receive those comments.

Mr. SHIMKUS. Ms. Taylor?

Ms. TAYLOR. Yes, we did submit our ads in accordance with the regulations, to the FDA. On occasion, we did receive comments, which we addressed with the FDA and had an ongoing dialogue with them. To give you a specific example of something that we had changed, one word in particular, non-myeloid cancers, which referred to the indication, was felt to be unclear to the consumers, and so this was adjusted to refer to patients with many types of cancer.

Mr. SHIMKUS. Was this an advisory opinion, or were these responses after the ads were already run?

Ms. TAYLOR. These were responses after the ads were run.

Mr. SHIMKUS. Mr. Chairman, I think that is all I have right now.

Mr. STUPAK. Mr. Whitfield for questions.

Mr. WHITFIELD. Thank you, Mr. Chairman.

Mr. Khanna, the phrase or term "enhanced" is used to identify the clinical trials as it related to Vytorin. Is that correct?

Mr. KHANNA. Yes, that is a specific trial for Vytorin.

Mr. WHITFIELD. And my understanding that the ad that Merck/Schering-Plough used relating to Vytorin, there was never any question about the truthfulness relating to the LDL cholesterol being lowered. Was that ever in dispute about the truthfulness of that aspect?

Mr. KHANNA. No, that was confirmed in our FDA-approved label and also confirmed in the enhanced study.

Mr. WHITFIELD. But the part of the ad that was in dispute related to cardiovascular outcomes. Is that correct or am I wrong there? What part of the ad was in dispute? Did it relate to the cardiovascular outcomes of using the drug?

Mr. KHANNA. Are you referring to the most recent letter that we received from the FDA?

Mr. WHITFIELD. Yes.

Mr. KHANNA. We initially sent our ads to the FDA. We got comments from the FDA on our ads, made those changes based on the FDA comments, and we ran those ads. Most recently, on January 23 of this year, we received a change of opinion from the FDA, so they have changed their opinion on some of the comments that they have, and would like us to consider putting a disclaimer about outcomes, that Vytorin does not have outcomes above simvastatin, which is a component of Vytorin. So we have just received those comments, and now we are working with the FDA to try to address those comments.

Mr. WHITFIELD. I don't remember the details of this, but wasn't there some issue relating to the relating to the release date of information of the enhanced study, and did that affect the change-of-opinion letter?

Mr. KHANNA. Sir, I am not sure what prompted the FDA's change of opinion letter. The letter came to us this year on January 23, so we are going to work with them to accommodate those changes.

Mr. WHITFIELD. But did your company delay the release of the enhanced study?

Mr. KHANNA. No, sir. I can tell you that the main debate that occurred around the Enhance study was around the quality of the data, and there was a significant scientific debate about the quality

of the data. I witnessed some of that debate. There were pros and cons to that debate. Ultimately, Merck/Schering-Plough did take steps to ensure that the quality of the data was there and to ensure that the data was meaningfully analyzed prior to it being presented, and that did take longer than we anticipated.

Mr. WHITFIELD. Now, Mr. Sage, on the Lipitor ad, I know that Lipitor has been studied for many, many years and has gone through hundreds of clinical trials, including use of thousands of patients, so your ad, there was never any questions about the truthfulness of the comments relating to the LDL—lowering of it, right?

Mr. SAGE. That is correct.

Mr. WHITFIELD. So the only issue relating to your ad was about Dr. Jarvik being in the ad, is that correct?

Mr. SAGE. That is correct, Mr. Congressman.

Mr. WHITFIELD. And the only issue there was that, one, he was paid, and two, he was not a practicing physician. Is that correct?

Mr. SAGE. Correct.

Mr. WHITFIELD. And your company made the decision to just pull the ad, is that correct?

Mr. SAGE. We ultimately made the decision to pull the ad. Our intent was never to misportray Dr. Jarvik. We took steps notto do that, but ultimately, there were misimpressions, so we decided to pull the ad.

Mr. WHITFIELD. But Lipitor is clinically proven to reduce the risk of heart attack?

Mr. SAGE. Yes, that is one of our indications: heart attack and stroke.

Mr. WHITFIELD. And do more cardiologists prescribe Lipitor than any other medication?

Mr. SAGE. They do, yes, sir.

Mr. WHITFIELD. OK, I have no further questions.

Mr. STUPAK. Is Mr. Walden not here? Mr. Ferguson.

Mr. FERGUSON. Thank you, Mr. Chairman. I appreciate your courtesy in allowing me to sit in here. I have been a longtime member of this subcommittee until recently, so it is nice to be back, and thank you for your courtesy in bringing me back.

Mr. Sage, was the Ford F150 truck the best-selling truck in the world before they started advertising? I am kidding. I thought a little levity might help. I am sorry. Thank you and our witnesses for being here. I appreciate it. I wanted to start with Ms. Taylor. Thanks for being here to discuss Procrit and the advertisements for Procrit. I am an open book. I just want to be clear up front. I am biased when it comes to Procrit. I lost my mother about 5 years ago to bone marrow cancer. She had cancer for about 6 years, and when she was first diagnosed, they gave her about a year to live. She ended up living 6 years. She got to meet three of her grandchildren over the course of that time. It was a great miracle in our family. But obviously, through extensive chemo and other cancer treatments, she was also someone who took Procrit, and some of the best days we had with my mom was when she was benefitting from the benefits of Procrit, so first of all, thanks for producing the product. No drug is perfect, but certainly in our family's case, it did a lot of good.

So just with that full disclosure, I understand the ads for Procrit changed over the time that you had them on the air. And I am not sure that some of the ads that we have heard about today give a full picture of the ads that aired over the course of time. Can you very briefly just talk about the reasoning that you had, over time, for changing the ads as you did?

Ms. TAYLOR. Most of the changes that were made in the ads were specifically, I believe, to clarify the condition for the consumer. So chemotherapy-induced anemia, as a term, is very difficult for a consumer to understand. Anemia, in fact, can be very difficult for a consumer to understand. The key symptoms of anemia, however, such as fatigue and weakness, are very apparent to them, so advertisements, then, tended to focus towards these key symptoms representing anemia, that would allow a patient to recognize them, and in consequence, then, seek guidance from his physician to talk about the symptoms.

In fact, not having seen the study from Dr. Day before, it was, I think, very reassuring and gave us a degree of confidence that these ads did talk and represent anemia in a definition that patients would understand and were well represented.

Mr. FERGUSON. So I know some of the criticism of your ads have been because of the discussion of symptoms. I am not a doctor. I am not a medical expert, but I know that, particularly in the case of anemia, as we saw in my mother's case, it is diagnosed, in part, by the presence of the symptoms, and a lot of folks, particularly patients who are just tired. I think back to my mom's situation. She was just tired. She didn't want to complain about just being tired when she was a cancer patient, so I would imagine that educating people like my mom or others about symptoms that might come with a more serious medical condition, rather than the fact that maybe they were just up late talking to kids or grandkids the night before would have something to do with whether or not they are getting the proper medical treatment. Is that correct?

Ms. TAYLOR. That is correct. And I think we need to be careful about what we are talking about here, because these were not correcting their anemia so that they could perform strenuous exercise. These were, in many cases, everyday acts of living that enabled them to carry on just a normal life while they are going through one of the most traumatic and invasive experiences in their life, which is to undergo chemotherapy.

Mr. FERGUSON. As far as you know, did your ads raise the awareness in the patient community that their symptoms might be caused by anemia?

Ms. TAYLOR. Yes, we believe it did. In fact, that is why we discontinued our ads in 2005. From our research, we believed that there was a sufficient understanding of these symptoms and recognition of them as being related to anemia. Roughly 6 to 7 out of 10 patients with chemotherapy will suffer from debilitating anemia through the course of treatment.

Mr. FERGUSON. Thanks, Mr. Chairman. I look forward to round two.

Mr. STUPAK. Thanks to the gentleman. Mr. Dingell for questions?

Mr. DINGELL. These are questions to our witness from Merck/Schering-Plough. Mr. Khanna, is it true that the enhanced study ended in April 2006?

Mr. KHANNA. Sir, the study was clinically completed in April 2006.

Mr. DINGELL. And is it also true that the Enhanced results were not released until January 2008. Is that correct?

Mr. KHANNA. Sir, there was a significant scientific debate about the quality of the data.

Mr. DINGELL. Now, the Enhance study showed no difference between Vytorin and Zocor in cholesterol build-up. Is that correct?

Mr. KHANNA. It showed no difference in the thickness of the carotid artery as measured by imaging, and we are talking about fractions of a millimeter difference here, which in part was some of the reason for the some of the quality questions, to really go through a better understanding of this data, and that was a significant scientific debate.

Mr. DINGELL. Now, between April 2006 and January 2008, Vytorin was advertised to the public in television ads. Is that correct?

Mr. KHANNA. It was advertised between September of 2004 through January of this year.

Mr. DINGELL. Now, in that period of time, Vytorin reached $5 billion in sales. Is that correct?

Mr. KHANNA. That is correct.

Mr. DINGELL. So Vytorin was marketed to the public while an important study showed that it was no more effective at cholesterol buildup than a generic drug that was delayed by the company for nearly 2 years, is that correct?

Mr. KHANNA. Sir, the study showed no difference in thickness of the carotid artery as measured by imaging. It did show that we lowered cholesterol more than simvastatin, consistent with our label, and it also showed that our drug was safe and well tolerated, consistent with our label.

Mr. DINGELL. So now, it is also true that FDA ultimately decided that these Vytorin DTC ads needed to be changed because they were misleading. Is that not so?

Mr. KHANNA. Sir, we did receive a change-of-opinion letter from FDA on January 23 of this year. Our FDA ads have all been reviewed by the FDA. We have received comments from the FDA and incorporated those comments into our ad.

Mr. DINGELL. But it is true, is it not, that FDA decided that these Vytorin ads needed to be changed because they were misleading. Yes or no?

Mr. KHANNA. We received a change-of-opinion letter from the FDA on January 23.

Mr. DINGELL. Now, Ms. Taylor, on March 9 of 2007, FDA issued a black box warning on the Procrit label, did it not?

Ms. TAYLOR. That is correct.

Mr. DINGELL. Along with the warning, FDA amended the Procrit label, removing all efforts to the improvements of quality of life in the cancer setting, did it not?

Ms. TAYLOR. I believe that is correct, yes.

Mr. DINGELL. On November 8, 2007, FDA once again strengthened the black box warning on the Procrit label. Is that correct?

Ms. TAYLOR. That is correct, yes.

Mr. DINGELL. Are you familiar with the findings in the February 27, 2008, issue of the Journal of the American Medical Association, concerning the risks of Procrit?

Ms. TAYLOR. I believe I am, yes.

Mr. DINGELL. Now, isn't it true that study researchers reported findings which demonstrated that even when used as directed, Procrit and other erythropoeisis-stimulating agents, or ESAs, put cancer patients at nearly 57 percent increased risk of blood clots? Yes or no?

Ms. TAYLOR. I don't have the article in front of me. I am sorry. I am not aware of that specific reference.

Mr. DINGELL. Well, are you saying yes or no or you don't know?

Ms. TAYLOR. I am saying I don't know.

Mr. DINGELL. Now, isn't it true that study researchers also found that Procrit and other ESA increased the death risk in cancer patients by about 10 percent? Is that true or not?

Ms. TAYLOR. I would have to check on that for you, sir.

Mr. DINGELL. All right, and they also found that Procrit and other ESAs could actually enhance cancer growth at the same doctors were using other drugs to control the disease. Is that not true?

Ms. TAYLOR. I would have to check that as well, sir.

Mr. DINGELL. Are you prepared to state under oath that Johnson & Johnson's national DTC advertising campaign, touting Procrit for fatigue relief, was unrelated to overuse or medically unnecessary use of Procrit in the years 1998 to 2005?

Ms. TAYLOR. Yes, sir, I am.

Mr. DINGELL. In your testimony, you stated that Procrit ads all communicated the same theme, essentially that anemia can cause fatigue and weakness, and Procrit may alleviate these symptoms. Is that correct?

Ms. TAYLOR. What we did talk about was that anemia was a key side effect of chemotherapy and that fatigue and weakness are key symptoms of anemia that are recognized by patients.

Mr. DINGELL. So then the Procrit ads promoted the notion that Procrit improves the problem of fatigue and the quality of life. Is that not so?

Ms. TAYLOR. What they did do was ask patients who were undergoing chemotherapy and who experienced fatigue and weakness to seek advice from their doctor about their symptoms and allow the doctor to make a decision at that point.

Mr. DINGELL. Now, these ads all featured weary, tired caner victims who regained their looks, energy and zest for life after using Procrit. Isn't that so, yes or no?

Ms. TAYLOR. I believe the ads accurately represented the community that was being treated by the product.

Mr. DINGELL. The tagline for these TV was "strength for living." Is that correct?

Ms. TAYLOR. That is correct.

Mr. DINGELL. Now, the FDA has repeatedly denied your company's application for a quality of life indication. Is that not true?

Ms. TAYLOR. The FDA has not approved a quality of life indication from Procrit. That is correct.

Mr. DINGELL. Now, Procrit was not an FDA-approved device to treat weakness or fatigue. It was approved for the treatment of anemia. Is that not true?

Ms. TAYLOR. It is approved for the treatment of chemotherapy-induced anemia. That is correct.

Mr. DINGELL. Now, is J&J or Ortho Biotech considering voluntarily removing Procrit from the market due to all of the controversy surrounding the safety of the drug?

Ms. TAYLOR. No, sir, we are not.

Mr. DINGELL. You are not considering that. Now, some final questions for the panel. Ladies and gentlemen, just to each of you, and we will start on your right and on my left. Will you agree to follow the AMA guidelines regarding the use of actors and health professionals in DTC ads? Sir?

Mr. SAGE. Mr. Congressman, I am not in a position to decide policy for Pfizer. That being said, as the team leader for Lipitor, if we were going to do this ad again, which we are not planning to do, I certainly would recommend it.

Mr. DINGELL. Sir?

Mr. KHANNA. Our ads are consistent with Pharma guidelines, and I believe Pharma guidelines are very similar in many cases to the AMA guidelines.

Mr. DINGELL. And ma'am?

Ms. TAYLOR. Yes, sir. Our guidelines as well are very consistent with the Pharma guidelines, and we would follow those explicitly.

Mr. DINGELL. So you are telling me that you are not going to follow AMA guidelines?

Ms. TAYLOR. No, our guidelines are consistent with the Pharma guidelines, and the Pharma guidelines are consistent, I believe, with the AMA recommendations.

Mr. DINGELL. Now, yes or no, starting again on your right on my left. Will your company agree not to market products in DTC ads until the completion of a valid outcome study? Yes or no?

Mr. SAGE. Mr. Congressman, in the case of Lipitor, which is what I am here to speak about today, we have well-validated outcome studies, so for Lipitor, yes.

Mr. DINGELL. Sir?

Mr. KHANNA. Sir, our ads focus on the points of lowering bad cholesterol, focus on the importance of diet, and focus on the fact that Vytorin does lower bad cholesterol. We believe that these are important, not only from a public health perspective, but lowering bad cholesterol, this is the cornerstone of heart disease prevention, and we believe it is important to continue to do that in a balanced an appropriate way and we will review what we——

Mr. DINGELL. I don't understand. Is that a yes or a no.

Mr. KHANNA. Sir, we believe it is important to continue to communicate the importance of lowering bad cholesterol.

Mr. DINGELL. I am still trying to understand. Is that a yes or no?

Mr. KHANNA. Sir, we are going to continue to communicate the importance of lowering bad cholesterol, as well as diet, and Vytorin as an option.

Mr. DINGELL. Now, ma'am, will your company agree not to market products in DTC ads until completion of a valid outcome study, yes or no?

Ms. TAYLOR. In speaking for Ortho Biotech, sir, we would be unlikely to be doing DTC advertising without valid clinical outcome studies. That is correct.

Mr. DINGELL. Now, this should be a fairly simple question. Pharma has issued guidelines on this subject which require a moratorium on DTC ad until physicians are adequately educated about the risks and benefits of the new drug. Starting on your right and my left, sir, will you follow the Pharma guidelines, yes or no?

Mr. SAGE. Pfizer does follow the Pharma guidelines and has its own more stringent internal guidelines, so yes, sir.

Mr. DINGELL. Sir?

Mr. KHANNA. We do feel it is important that physicians have experience with the drugs before we advertise, and in the case of Vytorin, physicians have experience with both Zetia as well as simvastatin.

Mr. DINGELL. All right. Ma'am?

Ms. TAYLOR. We did not advertise Procrit in DTC for a 5-year period after it was first approved, but for future products, we believe an adequate period, which may depend on the product and the condition being treated, but an adequate waiting period is most necessary, yes, sir.

Mr. DINGELL. These are simple yes-or-no questions again. If you please, sir, will your company market products in DTC ads for off-label uses, yes or no?

Mr. SAGE. Pfizer's position is that we market claims that are consistent with our label. Our new ads are pre-cleared. They are reviewed, and it is our belief that it should be within our label. Yes, sir.

Mr. DINGELL. Are you telling me yes, or are you telling me no?

Mr. SAGE. I am telling you yes.

Mr. DINGELL. You are telling me no. How about you, sir?

Mr. SAGE. No, sir. I said yes, to clarify.

Mr. DINGELL. You are saying yes. Sir?

Mr. KHANNA. If I may just ask you to repeat the question. There was a little confusion between the answer and the question.

Mr. DINGELL. Ma'am, yes or no?

Ms. TAYLOR. I was asking for clarity around the question as well. Would you mind repeating the question sir?

Mr. DINGELL. The question: will you agree not to market products in DTC ads for off-label uses?

Ms. TAYLOR. Yes, sir. We agree not to market products for off-label uses.

Mr. KHANNA. I agree. We will not market products for off-label use. Our promotion will be consistent with our FDA-approved label.

Mr. DINGELL. All right, now, FDA has a phone number of MedWatch. Will your company add to the ads that you are putting the notation that FDA has this 1-800-MED-WATCH phone number to be included in your DTC ads?

Mr. SAGE. Mr. Congressman, as I said, I am not in a position to decide that policy for Pfizer. I would certainly take that recommendation back.

Mr. DINGELL. Sir?

Mr. KHANNA. I will take that recommendation back for consideration.

Mr. DINGELL. Ma'am?

Ms. TAYLOR. Again, I am not in a position to qualify that for the entire company, but we most certainly would look at it.

Mr. DINGELL. So I haven't got any yesses. I have we will take it under advisement. Is that what I am being told here?

Mr. SAGE. Yes.

Mr. KHANNA. Yes.

Ms. TAYLOR. Yes.

Mr. DINGELL. Maybe you would like to select one of your number to tell me what would be your objection to adding that to your ads? What would be the objection to that, starting on your right? You obviously have a concern which says that this is not something that we want to do. What is it?

Mr. SAGE. My only concern is personal, Mr. Congressman. As I said, I am not in a position to make that decision for the company. It is not a question of whether or not we take adverse events seriously.

Mr. DINGELL. Sir?

Mr. KHANNA. Sir, it is something we want to evaluate. For me, but what is most important is that we promote what is consistent with our label, that it is accurate information, and what motivates patients to take an action to see their physician, so we are going to do that in the appropriate, balanced manner.

Mr. DINGELL. Ma'am?

Ms. TAYLOR. Yes. I am not in a position to be able to make that position here, but from a personal perspective, what is important is that patients have access to report that, and all of your current ads do have patient reporting number to report many adverse effects. So in the meantime, there is a mechanism with our advertising to follow that.

Mr. DINGELL. Thank you. Mr. Chairman, the thought occurs to me that maybe we need somebody who can really speak on behalf of the companies and just, perhaps, this committee should have a proper hearing in which we bring back the presidents of the companies, because I think that they could probably respond to these questions in a little more helpful fashion. And I thank you, Mr. Chairman for your courtesy, and if I have any time left, I will certainly yield to my good friend.

Mr. SHIMKUS. Just as you address that, a lot of things have been debated about the FDA did in this process because a lot of this stuff ran through their process and the question was why they weren't here. If we are going to do that, I would think the FDA would be another group to bring back to see what they knew and when they knew it and how they knew it and the like.

Mr. STUPAK. We are going to have votes here pretty quick. Let us shoot around a couple more questions if we can. I know I have some more questions.

Mr. Sage, just so there is no misunderstanding here, the issue with the Lipitor ad is not whether it was indicated that Mr. Jarvik was compensated, but more importantly it was that people had a hard time remembering the side effects and the way that you struc-

tured the ad so they did not know what it was. In fact, Dr. Day showed that people wildly misrepresented the need for blood test while taking Lipitor. Don't you think the serious side effects of these drugs should also have equal airing with the benefits of these drugs in the ads?

Mr. SAGE. Mr. Chairman, I think it is obviously important to communicate the side effects as well as the benefits in these ads. I also want to point out——

Mr. STUPAK. In an equal manner? Dr. Day sort of destroyed your ad in the way you placed your side effects.

Mr. SAGE. Mr. Chairman, all of our ads are reviewed internally. Many of those ads were reviewed by the FDA. They are accurately balanced.

Mr. STUPAK. Did you ever have a cognitive assessment made on your ads.

Mr. SAGE. No, we did not. I was not aware of the cognitive assessment. It was very enlightening. Thank you.

Mr. STUPAK. Mr. Khanna, today there is a news report that is running in the Wall Street Journal, stating that Schering-Plough has been asked to submit documents to the Justice Department on your Enhance study. Is that correct?

Mr. KHANNA. I am not aware, sir.

Mr. STUPAK. OK, it just hit today. So I guess I am kind of wondering if it was on Enhance study or on the stock sales. You don't know anything about it?

Mr. KHANNA. I don't know.

Mr. STUPAK. All right. Let me ask this question to you. In Vytorin, it appears that this is what we were talking about earlier about as an emerging science. You were going for a rare population that you were targeting, were you not?

Mr. KHANNA. No, sir, all people have cholesterol that you inherit as well as——

Mr. STUPAK. Right, but what about your Enhance study? Wasn't that targeted at people who not only have cholesterol but whose family history would suggest they have cholesterol problems?

Mr. KHANNA. No, sir.

Mr. STUPAK. Well, why the hot dog and Uncle Frank, then?

Mr. KHANNA. No, sir, the Enhance study was a very specific patient population called heterozygous FH who was predisposed to having very high levels of cholesterol.

Mr. STUPAK. Because of family history?

Mr. KHANNA. Well, they have very high levels of cholesterol, but everybody gets cholesterol from family.

Mr. STUPAK. I don't disagree with you. You make two claims. Number one, you are going to fight cholesterol. Number two, you are going to go after those folks whose family history produces cholesterol, correct? That is your Enhance study, right?

Mr. KHANNA. What we are saying is that you get cholesterol from two sources. You get it from food that is high in cholesterol, and inheritance.

Mr. STUPAK. Right, and it was a small study, and you conducted the Enhance trial because of this, for those who have a very high level of LDL cholesterol, right?

Mr. KHANNA. No, sir, we got approved based on our ability to lower bad cholesterol. That is the way that the FDA approves drugs in this marketplace.

Mr. STUPAK. OK, so it is just bad cholesterol, so why are you having the frank hot dog and Uncle Frank or Virginia and Virginia ham?

Mr. KHANNA. We are tying to do a few things. One, we are trying to say that lowering bad cholesterol is important. Two, we are trying to reinforce diet. Three is we are tying to say you get bad cholesterol from food that is high in cholesterol, such as a hot dog, or your mom and dad, because what we found is that if we can educate people that you get high cholesterol——

Mr. STUPAK. So your Enhance study wasn't meant to reduce cholesterol but also to reduce the blockages. Wasn't that the purpose of your Enhance study?

Mr. KHANNA. Sir, the purpose of the Enhance study was to look at the effect on the carotid artery and compare Vytorin to simvastatin, and what we found in there was that there was no difference in these images.

Mr. STUPAK. So that part wasn't proven, and that is why the study is in question here, right? The results of your study, what you thought it would be, and what it ended up being, was two different things.

Mr. KHANNA. We did plan for a range of options.

Mr. STUPAK. What you thought the study was going to show, it did not show that. In fact, it took you 2 years to release that study, did it not?

Mr. KHANNA. Sir, there was a very rigorous scientific debate about the quality of the data.

Mr. STUPAK. OK, it took you 2 years to release it, right?

Mr. KHANNA. I am not a scientist, but I witnessed that debate, and there were pros and cons about that debate.

Mr. STUPAK. Why don't you go to the exhibit book. We have several emails from Merck/Schering-Plough as well as from coordinators of the Enhance study that shows the results were delayed. That is exhibit 22. It shows that the results were delayed several times, even against the wishes of the principal investigator. Do you know what the delays were in the Enhance trial?

Mr. KHANNA. Sir, I know that there were significant steps taken to look at the quality of the data, and I know that that process around the quality of the data and to ensure that the data could be analyzed meaningfully did take longer than anticipated.

Mr. STUPAK. Let us go to exhibit 19. This is a print ad for Vytorin, submitted to the FDA. Each fact is annotated to a reference verifying its truthfulness. This paragraph about the two sources of cholesterol is attributed to a Web site called aboutyourcholesterol.com. That Web site actually advertises for a mail-order dietary supplement to lower cholesterol, so it seems to me that two sources of cholesterol is the cornerstone of Vytorin's ad, and yet you reference a commercial dietary supplement Web site to support the FDA application. Why not publish a scientific study or an internal research document?

Mr. KHANNA. Mr. Chairman, the reference to this Web site was clearly an error, but Vytorin does treat the two sources of cholesterol.

Mr. STUPAK. All right, so that was a mistake you made.

You submit your ad to the FDA, but yet it takes you 2 years to release the study. So why wouldn't you just release the study when it was completed to the FDA like you did your ad? What is more important? The ad or the results of your study?

Mr. KHANNA. Sir, this was a scientific issue and it may——

Mr. STUPAK. Well, wait a minute, submitting something to the FDA is not a scientific issue. In fact, you are required to submit your studies to the FDA. That is a legal requirement.

Mr. KHANNA. This is a question of the quality of the data and to ensure that that data can be analyzed. It was the details of the science around the enhanced study and making sure that quality is there. Ultimately, MSP did take steps to ensure the quality of the data and to make sure that it could be analyzed meaningfully prior to unblinding the data, and that did take longer than we anticipated.

Mr. STUPAK. My time is up. Mr. Shimkus? I still want to get to Ms. Taylor. I have still got a number of questions for Ms. Taylor. But go ahead, I have gone a little bit over my time.

Mr. SHIMKUS. Yes, Mr. Chairman, I am going to yield to Mr. Ferguson. We are having competing hearings, and he would like to get upstairs if that is OK.

Mr. FERGUSON. Thank you very much for your courtesies, both of you. Mr. Khanna, just to continue on this line of questioning, I understand that there have obviously been some questions about what enhanced actually showed. My understanding is that while enhanced showed no significant difference in the impact on the artery wall thickness between Vytorin and the simvastatin, the study also showed what you already knew, which was that Vytorin lowers LDL bad cholesterol better than a statin alone. Is that correct?

Mr. KHANNA. That is correct.

Mr. FERGUSON. And was enhanced designed to study or to measure the effect that Vytorin has on cardiovascular outcomes?

Mr. KHANNA. No, sir, it wasn't designed or intended to look at heart attacks or strokes.

Mr. FERGUSON. So the last patient visit for the Enhance study was in April 2006. The results were released earlier this year, so a little less than 2 years. With any clinical trial, we know that immediately following the last patient visit, there is a process of quality control, analysis of the data, to ensure that the data is reliable. You have unblinded the results. You have to analyze the results. My understanding is that for a number of reasons, with enhanced in particular, with regard to the data, including the methodology that was used to measuring, that quality-control process took a little longer than expected.

Mr. KHANNA. That is correct.

Mr. FERGUSON. How much longer?

Mr. KHANNA. I can't give the exact amount of time, but the scientists did feel that getting the quality-control questions right was very important, and there was a robust debate among many sci-

entists about the quality issues, and untimely MSP did take steps to ensure that quality.

Mr. FERGUSON. Do you think you would have come under some heat if you released the study more quickly, and you found out later that the methodology or the data were insufficient or wrong somehow?

Mr. KHANNA. You know I can't comment on that.

Mr. FERGUSON. I could probably answer that question. I am going to say you are going to be damned if you did and damned if you didn't. Let me just be clear, did you know the results of the enhanced study while your ad for Vytorin was on the air?

Mr. KHANNA. No, sir, I was not made aware of the results of the Enhance trial until January the 8 of this year.

Mr. FERGUSON. And at that point, Vytorin ads were off the air. You had already chosen to take them off the air.

Mr. KHANNA. We took them off the air on January the 14th, but I was made aware of the study results on January 8 of this year.

Mr. FERGUSON. So you made the decision about the ads before you even had the results of the enhanced study?

Mr. KHANNA. I made the decision about the ads. It was on January the 14th, essentially the same date that we released the primary end-point results of the enhanced trial, via a press release. The reason I made the decision to stop the ads was mainly because there was already a lot of science discussion about enhance, as well as speculation about the results. Since we were releasing the primary end-point results, I didn't want the ad at the same time because I thought that there would potentially be confusion out in the marketplace, so I chose to stop the ad at that time.

Mr. FERGUSON. So just to be clear and backing up for a minute. I went through with my doc, my good cholesterol/bad cholesterol numbers, and essentially if your bad cholesterol number is high, it could be from what you eat, or it could be genetic, right?

Mr. KHANNA. That is correct.

Mr. FERGUSON. So it is possible that someone who has a great diet, someone who eats all of the right things still has a high level of bad cholesterol because of genetics. Is that possible?

Mr. KHANNA. That is absolutely correct, and that is part of the reason we wanted to educate on two sources, because if you have got a high diet——

Mr. FERGUSON. So even a person who thinks they are totally responsible—I only eat salad, I don't eat anything with any cholesterol in it, there is no reason that I should have a high level of bad cholesterol—could still be at risk for health consequences because they have a high level of bad cholesterol. That is possible, isn't it?

Mr. KHANNA. That is correct.

Mr. FERGUSON. And that person would probably benefit from knowing that high levels of bad cholesterol could come from more than the source of a diet.

Mr. KHANNA. That is correct.

Mr. FERGUSON. Thank you, Mr. Chairman.

Mr. STUPAK. Thank you, Mr. Ferguson. Mr. Shimkus for questions?

Mr. SHIMKUS. I think just a brief one. My friends on the majority have issued a number of letters about all of these studies, request-

ing information from you all. Are you still in the process of providing documents in response to these requests?

Mr. SAGE. We have complied with the Committee's request and continue to provide information as needed.

Mr. SHIMKUS. I mean we, as a committee, are still receiving information from you?

Mr. SAGE. If there is any new information to be had, you are going to receive it, yes.

Mr. SHIMKUS. Mr. Khanna?

Mr. KHANNA. Yes, we continue to comply with the Committee, and we are in an ongoing process of sending them information.

Mr. SHIMKUS. So is there any outstanding information that we still have yet to get to the Committee, based upon your product, that we are in the process of getting, or are you waiting for more requests from us?

Mr. KHANNA. No, we are just responding to the various requests that we are receiving.

Mr. SHIMKUS. Ms. Taylor?

Ms. TAYLOR. We have provided everything. That is my understanding.

Mr. SHIMKUS. In the last 4 months, give me an idea of how many documents you may have sent here. I will start with Mr. Sage. Do you have any idea of the number of documents?

Mr. SAGE. Two hundred and ninety thousand.

Mr. SHIMKUS. Wait, can you say that again?

Mr. SAGE. Two hundred and ninety thousand pages.

Mr. SHIMKUS. Two hundred and ninety thousand pages. Mr. Khanna?

Mr. KHANNA. I am told that it is in the same vicinity.

Mr. SHIMKUS. Two hundred and ninety thousand? Ms. Taylor?

Ms. TAYLOR. I don't have the specific number. I am sorry. My own understanding is that is a lot less.

Mr. SHIMKUS. Maybe a hundred thousand? I am just joking.

Ms. TAYLOR. I really don't know.

Mr. SHIMKUS. I mean that is a lot less than 290,000.

Ms. TAYLOR. I can find out for you, though, as soon as possible.

Mr. SHIMKUS. Do you know if all of the interviews of people involved in the studies are still being conducted, Mr. Sage?

Mr. SAGE. I am not sure I quite understand your question. In our case, we are not speaking about a study, so if you could clarify, that would be helpful.

Mr. SHIMKUS. Let me just go to Mr. Khanna, same question. Do I need to repeat it?

Mr. KHANNA. We believe there are still more interviews that are going to need to be conducted.

Mr. SHIMKUS. The chairman is saying there is going to be a lot more, so I am probably getting ready for 290,000 more pages.

Is it your understanding that this investigation is ongoing, Mr. Khanna?

Mr. KHANNA. Yes, that is my understanding.

Mr. SHIMKUS. I think just part of the concern on this side is that I think there is still information to be had, and I said this in my opening statement, but it is tough to do oversight and investigation when not all of the stats are in, not all of the documents. We don't

have the FDA here. I am new at this business, but that is part of this side's concerns about the process that we have today, but I think we have learned a lot, and I will probably learn more, so I am going to yield back my time, Mr. Chairman.

Mr. STUPAK. Thanks. In those 290,000 pages was there anything in there in which you looked at consumers to see if they understood the side effects of Lipitor, Mr. Sage, since that was one of Dr. Day's criticisms of your ads?

Mr. SAGE. We look comprehensively at what consumers took away from our advertisements, Mr. Chairman.

Mr. STUPAK. Right, and there was nothing in there about the adverse side effects, if they understood it, was there?

Mr. SAGE. There are no specific studies on that.

Mr. STUPAK. Ms. Taylor, I said I would get to you. I have a couple of questions for you. A year ago a public FDA advisory committee, Dr. Richard Hauser, FDA's chief oncologist, remarked that the FDA and the Office of Chief Counsel owed the American people an explanation why Procrit TV ads were allowed to run for 7 years. Ms. Taylor, are you aware that many of the experts inside and outside of the FDA consider the 7-year Procrit TV ad campaign to have been false and misleading because it constituted off-label advertising for the treatment of fatigue, which it is not approved for by the FDA.

Ms. TAYLOR. No, sir. In fact, my understanding is that we had a reassurance that during the period concerned, the FDA was satisfied that we complied with regulations.

Mr. STUPAK. I am talking about your advisement for fatigue. That is an off-label use of Procrit, isn't it?

Ms. TAYLOR. Our approved use for Procrit is chemotherapy-induced anemia.

Mr. STUPAK. Right, not for fatigue, right?

Ms. TAYLOR. And the symptoms of fatigue and weakness, which are cardinal symptoms of anemia were used to describe that for patient DTC.

Mr. STUPAK. In that exhibit book there, go to exhibit 39. Isn't it true that Ortho Biotech and Johnson & Johnson were repeatedly cited by the FDA for false and misleading advertising in connection with direct-to-consumer advertising of Procrit as a treatment for fatigue: exhibit 39, November 6, 1998 letter from the FDA to Johnson & Johnson, exhibit 44, June 30, 2000 letter from the FDA to Johnson & Johnson, in reference to promotional campaign for Procrit? The FDA wrote that the claims made throughout the promotional materials are in violation of Food, Drug, and Cosmetic Act and implemented regulations due to expanding the use of a product as a treatment for fatigue. Exhibit 50, dated 12/21/01, letter from the FDA to Johnson & Johnson, detailed "false and misleading aspects of Procrit advertising, including two direct-to-consumer broadcast TV ads Auntie Em and Big Boy Bed," and requested that Johnson & Johnson revise the advertising materials accordingly. "Claims or implications that Procrit treats weakness and fatigue or that Procrit increases strength are misleading. Procrit is indicative for the treatment of anemia for patients receiving chemotherapy for cancer." So how can you say that was not false and misleading, and

you kept within the FDA guidelines when you have exhibit 39, 44, and 50 that say just the opposite?

Ms. TAYLOR. These were all, my understanding is, part of an ongoing discussion that went on with the FDA, and after each of these letters there was further discussion, and we complied or agreed with the FDA——

Mr. STUPAK. Let me ask you this one. If you were receiving chemotherapy, you lose your hair, right?

Ms. TAYLOR. You can, right.

Mr. STUPAK. How come your ads don't have anyone in there that lost their hair to chemotherapy? I mean that is a real simple thing you could comply with to have a fair ad. In fact, I believe it is exhibit 50, the FDA said the models you were showing in your ads were not accurate because you had people who still had hair, and we know in chemotherapy you lose your hair. It is number two, December 21, 2001, exhibit 50, "The presentations are misleading because the patient models depicted are not representative of the general population of chemotherapy patients who would appear weaker and have hair loss among other side effects." That doesn't sound like a discussion to me. That is sort of a directive on how you should be doing your ad, and you never presented an ad with a person without hair.

Ms. TAYLOR. No, we didn't. I don't have the follow-up discussion, but I do believe that subsequent ads, which were agreed with FDA, and which did not have patients who had hair loss were accepted by FDA in a subsequent period.

Mr. STUPAK. Let me ask you this. You said you are pleased with your ads because people started to understand what edema was, in response to Mr. Ferguson.

Ms. TAYLOR. Anemia.

Mr. STUPAK. Anemia, not edema, OK. And you were here when Dr. Day showed that people didn't remember and understand edema.

Ms. TAYLOR. Yes, edema.

Mr. STUPAK. So why did you use a medical term like edema instead of using something people would understand like body swelling?

Ms. TAYLOR. Actually, we were pleased to see the very high level of recognition of the risks that we have——

Mr. STUPAK. Did you run your ads by anyone like Dr. Day for cognitive assessment? Anywhere in your company did you ever look to see if people understood the side effects of these drugs that you were promoting?

Ms. TAYLOR. I am not aware of specific research that was done to determine that, but in seeing Dr. Day's comments, it certainly gave us pause to look at specific expressions like edema in future advertisements.

Mr. STUPAK Anywhere in your advertising did you say that use of Procrit for cancer patients who had tumors that Procrit would be likely to enlarge those tumors and endanger the lives of those patients?

Ms. TAYLOR. No, that was not a specific warning in the ads.

Mr. STUPAK. But the FDA told you about that, and you didn't put that in there. Don't you think people should know that before they

take your drug, that in fact, it could worsen their condition, not make it better, by making the tumor swell more and shorten their lifespan?

Ms. TAYLOR. That is a theoretical concern that has been raised.

Mr. STUPAK. Well, it has been documented, right? I mean they documented how the tumors would swell. In fact, the greater the Procrit they got, the quicker the tumor swelled.

Ms. TAYLOR. I don't believe that that is accurate, but what we did do with the ads was we included all of the side effects that were significantly different from placebo.

Mr. STUPAK. That would be significantly different, wouldn't it, if you were a cancer patient and the tumors you had in your body swelled when you took Procrit? Wouldn't that be significant, especially when it shortens your life?

Ms. TAYLOR. These are significant results as measured in clinical studies, so the side effects that were there such as diarrhea and edema, those were significantly different to placebo.

Mr. STUPAK. Can you point to any of the documents that you submitted, anywhere, where the FDA approved Procrit for off-label use for fatigue or weakness in patients? Can you point to any one document of any use submitted to our committee?

Ms. TAYLOR. Procrit has been approved for chemotherapy-induced anemia. Our advertisements were specifically looking at using language that would be recognizable by a consumer such as——

Mr. STUPAK. So I take it your answer is no because you cannot point to an exhibit, as the FDA wrote to you in exhibit 39, 44, and 50, telling you not to use your ads for tiredness and for weakness. Do you have any letter from the FDA in all of those documents that you provided us that said you could advertise for that?

Ms. TAYLOR. In fact, all of the way through, there have been discussions with the FDA about——

Mr. STUPAK. I didn't ask about discussion. I asked about approval for the way you marketed Procrit for 7 years for an off-label use that was not approved for Procrit. Do you have any document that can show me that?

Ms. TAYLOR. We have consistently, throughout, had reassurances that the way we were communicating the symptoms of anemia, such as fatigue and weakness, was appropriate to the patient group that we were reaching with the DTC.

Mr. STUPAK. All right, so you disagree with what the FDA writes in exhibit 39, 44, and 50? That is all right. Mr. Shimkus, questions?

Mr. SHIMKUS. I am going to yield my questions.

Mr. STUPAK. Mr. Burgess is here. Questions?

Mr. BURGESS. I will on the next round.

Mr. STUPAK. We are on three, so Mr. Burgess?

Mr. BURGESS. Thank you, Mr. Chairman. I apologize for being late and coming in at the end of things here. We are also dealing with stem cells and the Ambassador to Mexico and Medicare payments, so there is always something going on.

On the issue that you were just discussing with the chairman, Ms. Taylor, with the studies regarding tumor growth, when did that come up? When did that become a concern for your company?

Ms. TAYLOR. In fact, the theoretical potential for growth was identified in the original label for Procrit.

Mr. BURGESS. Because when I saw the ad that was played at he beginning of this hearing many, many hours ago, Mr. Chairman, it was specific that it said that this is for non-hematologic tumors, is that correct?

Ms. TAYLOR. It is for non-myeloid.

Mr. BURGESS. Non-myeloid. Because there was concern for if it were a myeloid condition, that it might in fact be stimulatory. Is that correct?

Ms. TAYLOR. I am not aware of the exact reason for it, but it was a theoretical concern when we first had approval for the product.

Mr. BURGESS. Now, is there any indication as to which types of tumors might be so affected with the theoretic concern of increased rumor growth?

Ms. TAYLOR. I am not aware of specific tumor types that were identified at that point.

Mr. BURGESS. Are there, in fact, studies ongoing now to look into that and answer these questions?

Ms. TAYLOR. Yes, we are attempting to complete a very large study. It is very difficult to recruit for because of the very nature of it. And in trying to do a definitive study, such as a placebo-controlled study, it is very difficult to do in this patient population, but we are working closely with the FDA and believe that we have a design that will meet the needs to answer some of these questions.

Mr. BURGESS. And I realize that a retrospective study is always fraught with some difficulty, but has there been any attempt to retrospectively go back and mine the data and look at that basis?

Ms. TAYLOR. There is currently underway—a Cochrane Collaboration is doing a very large review of all of the data of the years. I think it is roughly about 15,000 patients experience that is in analysis now, and we should have that in the coming months.

Mr. BURGESS. Very good. On the issue of Procrit itself, was it ever approved for the indications of treatment of fatigue and improved quality of life?

Ms. TAYLOR. Procrit is approved for the treatment of chemotherapy-induced anemia. For the advertisements that we did with patients, we use the terms fatigue and tiredness as representative for patients' understating of the term anemia.

Mr. BURGESS. So you were referencing the symptoms of anemia?

Ms. TAYLOR. This was referring to the symptoms of anemia, such as fatigue and tiredness and also the reduction in red blood cells.

Mr. BURGESS. So the indication existed, then, for treating low red cell mass as a result of chemotherapy, and it really then kind of strains credulity to think that it's misleading if you talk about the symptoms of anemia and reduced red call mass as being those symptoms that you are trying to target with your treatment of anemia and reduced red cell mass.

Ms. TAYLOR. That is what we thought, yes.

Mr. BURGESS. That is what I would assume as well.

Dr. Khanna, let me just ask you a question, and again, I apologize to you for being late. On the issue of the Vytorin controversy that has been discussed today, I referenced in my opening statement that perhaps there is some good in just delivering the infor-

mation that cholesterol comes from two sources, that the average person with a diagnosis of hypercholesterolemia may not be aware of the fact that, yes, there are some things that they do that affects their cholesterol level, but there may be something thing that are embedded deep within their cells or their DNA or their family history that results in high cholesterol, so they may just be a benefit from even just stating that and providing that educational information to patients, is that not correct?

Mr. KHANNA. That is correct. We know that there are many patients that are diagnosed, but are untreated, that when you educate them that your cholesterol comes from two sources, it takes away one of the barriers, and one of the barriers is until they know that, they feel it is all their fault, so no matter how much they exercise and how much they exercise, they feel it still their fault. Once you educate them, this motivates them to at least have a conversation with their doctor about any additional treatments they should consider.

Mr. BURGESS. And just on an intuitive basis, to me it always made sense, the addition of those two compounds to fight high cholesterol levels. One of the difficulties with statins is that some people don't tolerate them as well because of side effects. Is it ever the case that you can use a lower level of statin by the combination with other medicines to achieve the desired result of lowering the cholesterol level?

Mr. KHANNA. That is correct. What Vytorin provides you is additional, significantly greater LDL lowering, and we have head-to-head studies to show that we have got greater LDL lowering than the three available statins that are on the market, as well as getting more patients to goal, so you could use a lower dose of the statin with Zetia to achieve additional benefits.

Mr. BURGESS. And currently, what is the level of LDL which is the upper limit that you want to be under?

Mr. KHANNA. Sir, that varies depending on your risk factors, but it could be anywhere less than 130, less than 100, less than 70, depending on your risk factors that you have.

Mr. BURGESS. But the overall trend as far as the recommendation of the medical community has been to recommend a lower number as the upper limit of normal, over the last 10 or 15 years' time. Is that not correct?

Mr. KHANNA. That is correct.

Mr. BURGESS. Very well. Mr. Chairman, I will yield back my time.

Mr. STUPAK. Thank you.

Since it came up, let me just ask this. It has come up by both sides here about the erectile dysfunction and when it should be adverted. And two of the makers are here of it. Mr. Sage, Viagra is made by Pfizer. Would you agree that we should pull those ads until later at night when it is not affecting young audiences?

Mr. SAGE. Pfizer's policy on advertising Viagra is to advertise it on shows that have at least 90 percent adult viewership.

Mr. STUPAK. OK, it is not a timeline. You do it based on viewership?

Mr. SAGE. It is based on viewership, yes, sir.

Mr. STUPAK. And Mr. Khanna? Schering-Plough has Levitra, right? And so would you agree to move your advertising where kids would not see it?

Mr. KHANNA. Mr. Chairman, I am the general manager of the joint venture. My responsibilities are solely on Vytorin and Zetia, so I cannot comment on other products for either parent organization.

Mr. STUPAK. OK, how about as an individual? Do you think we should be showing those ads during certain hours and there should be appropriate hours and inappropriate hours to show Levitra ads?

Mr. KHANNA. In my own opinion, I do have two young children, and I would not like to see ads like that during the times when kids are watching TV.

Mr. STUPAK. Mr. Shimkus.

Mr. SHIMKUS. Yes, I want to concur with the chairman. I am a First Amendment guy. I am schizophrenic on this whole debate, but even the 90-percent viewership, when you have on a major movie that PG-13, I think we really need to look at some of these movie channels, and some good stewardship would help go a long way.

Mr. FERGUSON. Mr. Chairman, could I concur on that as well, but I would also say that, as father of four kids under ten, I think we have similar concerns about any kind of advertising that is on TV. Certainly when we are talking about ED drugs, but we also know that there is a lot of trash on TV, and it is even tough when you are watching a ball game with you kids on the weekend, and I have to sit there with the clicker as soon as any ad comes because some ad for some trashy TV program that is on later in the week on that same station then comes on, and you are flipping the channel, and you are muting it, and it is like a test to see how quickly you can do it. So I absolutely agree that there are appropriate ads that should be on certain program or certain times of the day, but it is really, really tough, and it is certainly not unique to this industry or any other industry that as ads run that sometimes may be inappropriate for kids. And I absolutely agree that this is a problem, but it certain is a broader problem than we are talking about here. And I would certainly be delighted to work with you, Mr. Chairman, and the ranking member, and others if we are going to develop some sort of a proposal for this.

Mr. STUPAK. Thanks, and at the request of the minority, we will have another hearing on direct-to-consumer advertising, so maybe that could be a part of it.

Well, that concludes all of the questions. I want to thank all of the witnesses in this panel. They are free to go, and thank you for testimony today.

I ask unanimous consent that the hearing record remain open for 30 days for additional questions for the record. Without objection, the record will remain open. And I ask unanimous consent that the contents of our document binder be entered into the record. Without objection, the documents will be entered into the record. That concludes our hearing. Without objection, this meeting of the subcommittee is adjourned.

[Whereupon, at 3:50 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

DTC Drug Ads:

What Do People Understand & Remember?





Ruth S. Day / Duke University

House Energy & Commerce Committee
Hearing on DTC Ads / May 8, 2008

I am not here today

--as a nay-sayer….

--as a yea-sayer….

Instead

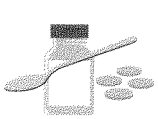
I am here to report

--research on how people understand and remember information in drug ads

This research was not funded

by any: --drug company
--ad agency
--advocacy group
--government agency

QUESTION:





How do people understand drug information?

ANSWER: With difficulty!

WHY:

--Heavy information load

--Complex/technical information

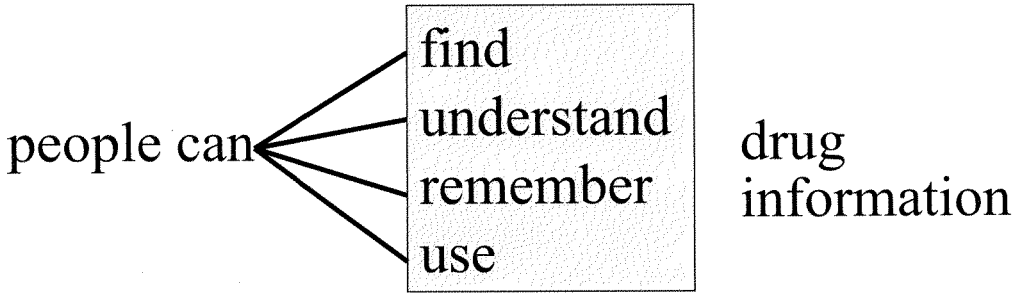
--etc.



--Cognitive Accessibility

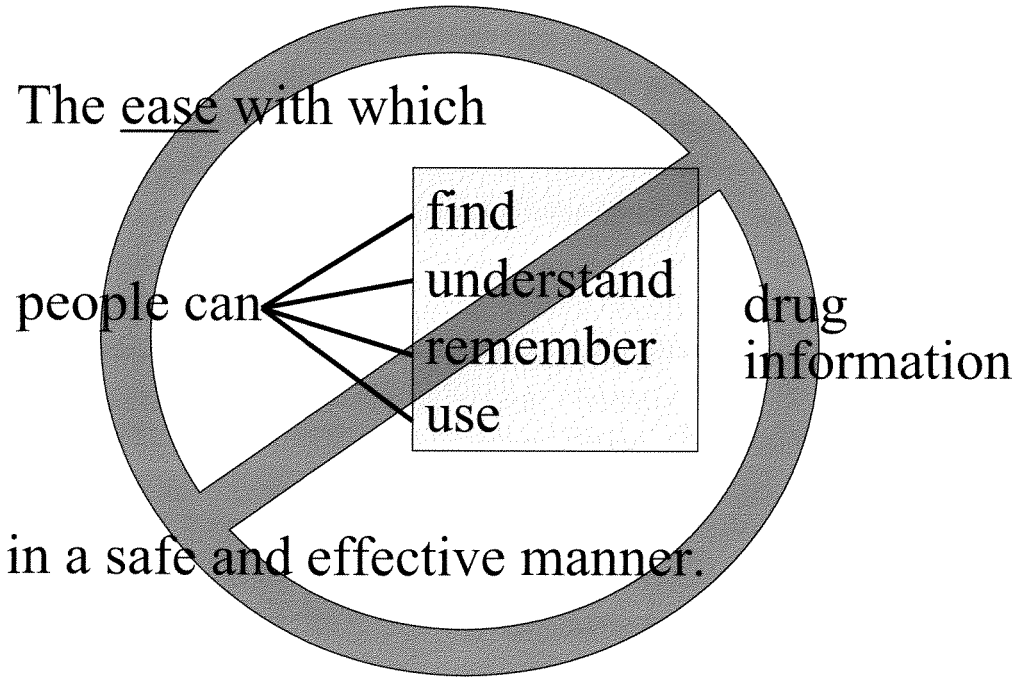
Cognitive Accessibility

The ease with which

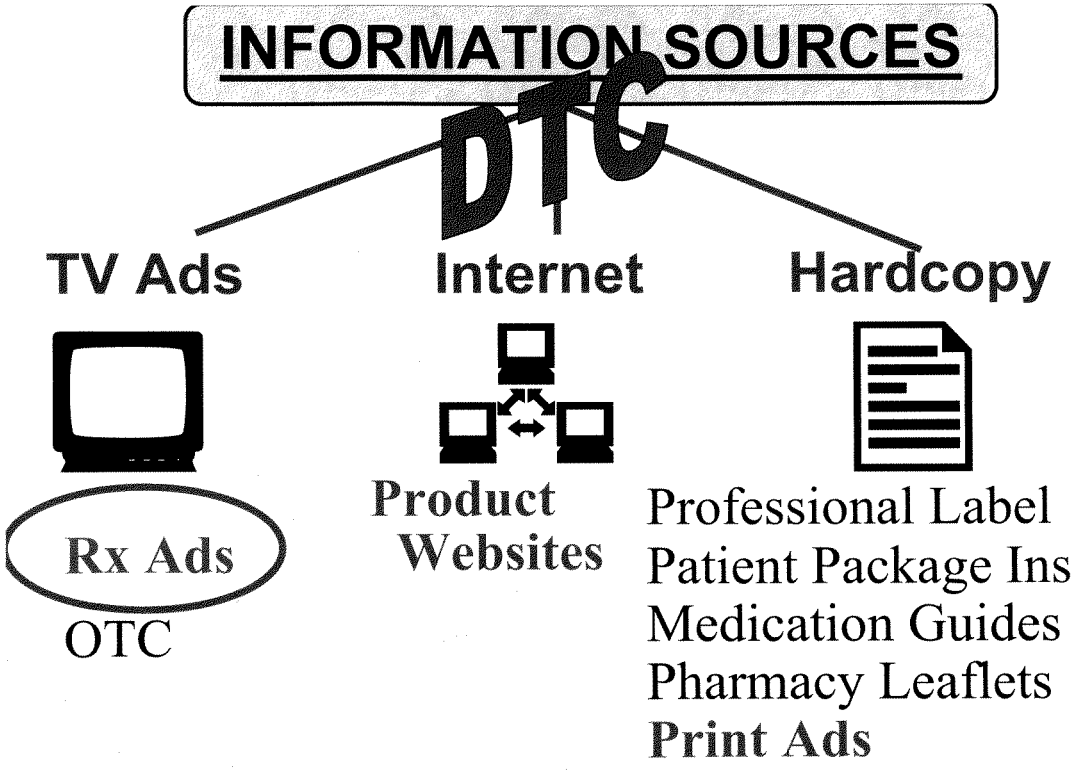


in a safe and effective manner.

Cognitive IN-Accessibility

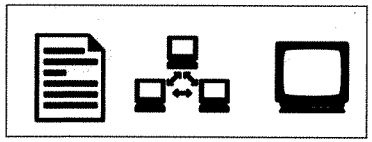


Ruth Day


INFORMATION SOURCES
DTC
TV Ads
Internet
Hardcopy
Rx Ads
OTC
Product
Websites
Professional Label
Patient Package Inserts
Medication Guides
Pharmacy Leaflets
Print Ads

BASIC APPROACH

Cognitive Analyses

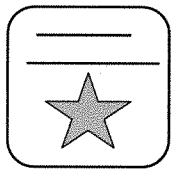


--Obtain quantitative measures

--Calculate "cognitive accessibility"

--Compare benefits vs. risks

Enhanced Version



--Same info

--Based on cognitive principles

Cognitive Experiments

Test effects on:

- **--Attention**
- **--Comprehension**
- **--Memory**
- **--Problem Solving**
- **--Decision Making**
- **--Behavior**

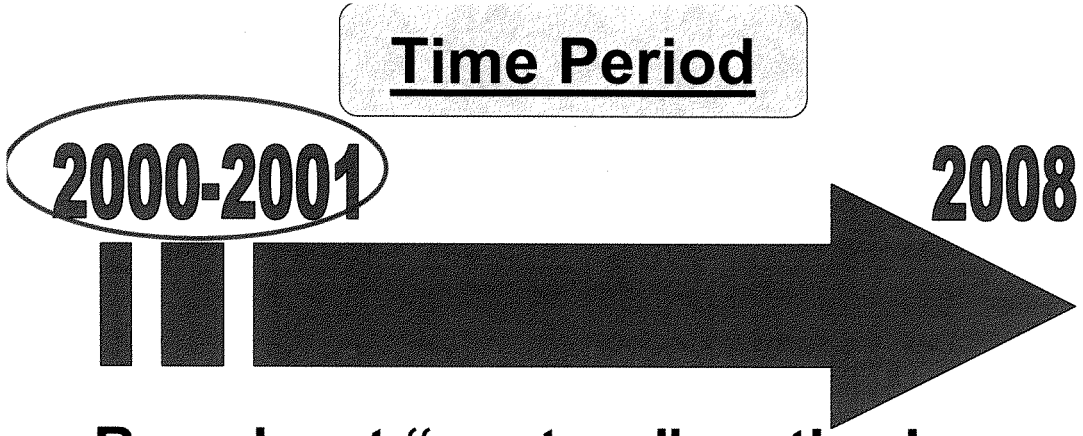
Health Outcomes

Ruth Day

COGNITIVE PRINCIPLES

- Language difficulty
- Chunking
- Location
- Speed
- Attention

Rx TV Ads
Rx
Ruth Day



Broadcast "capture" method

--record on daily basis
--capture embedded ads

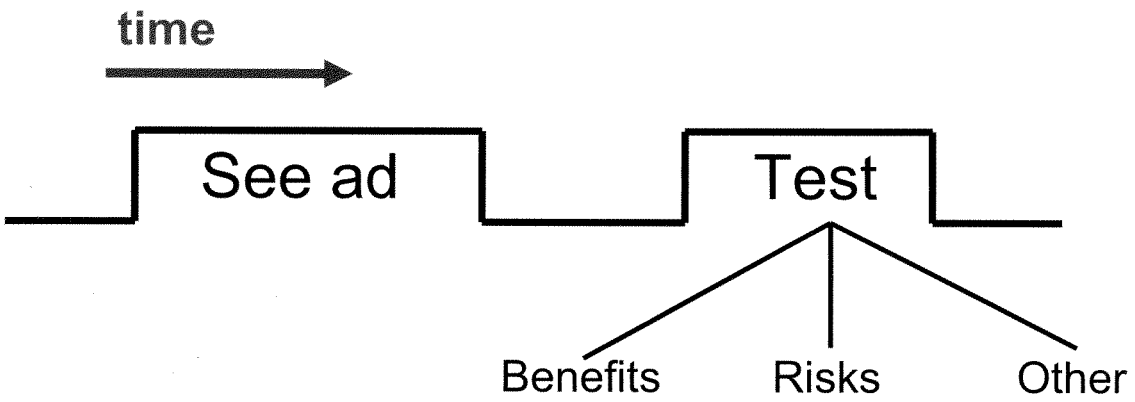
Therefore do not target:

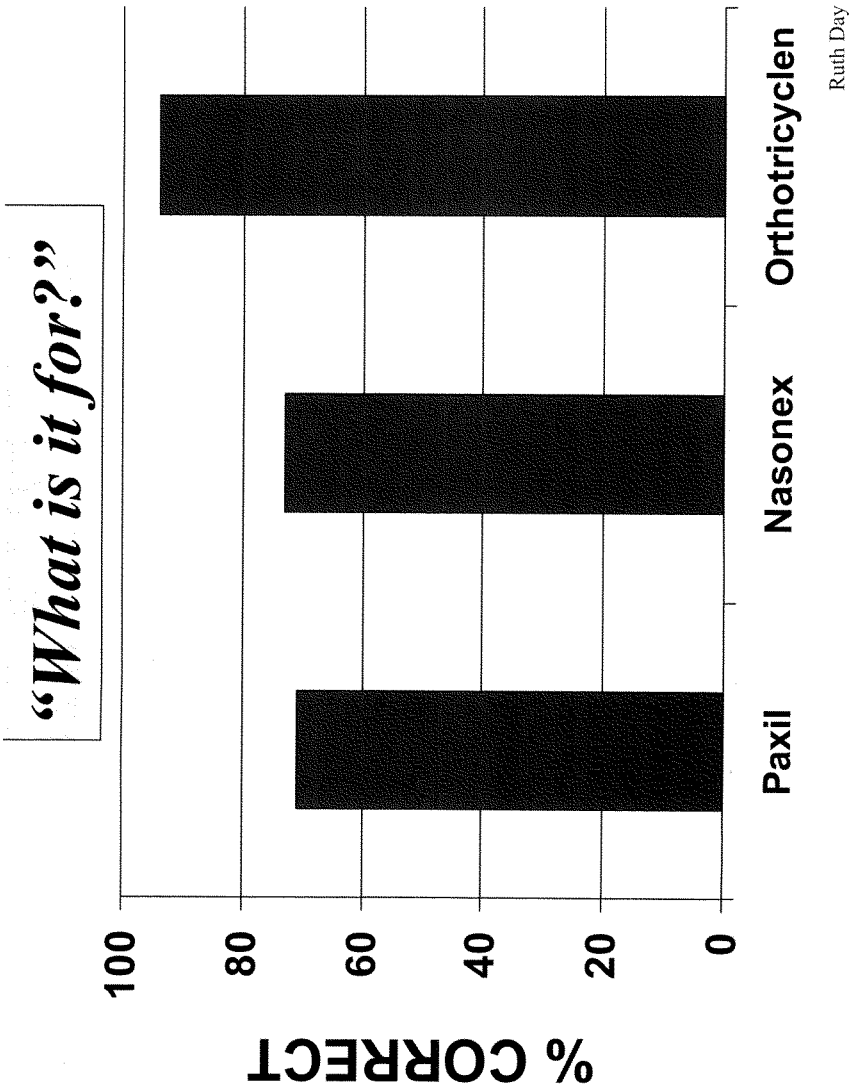
--specific health conditions
--specific drugs

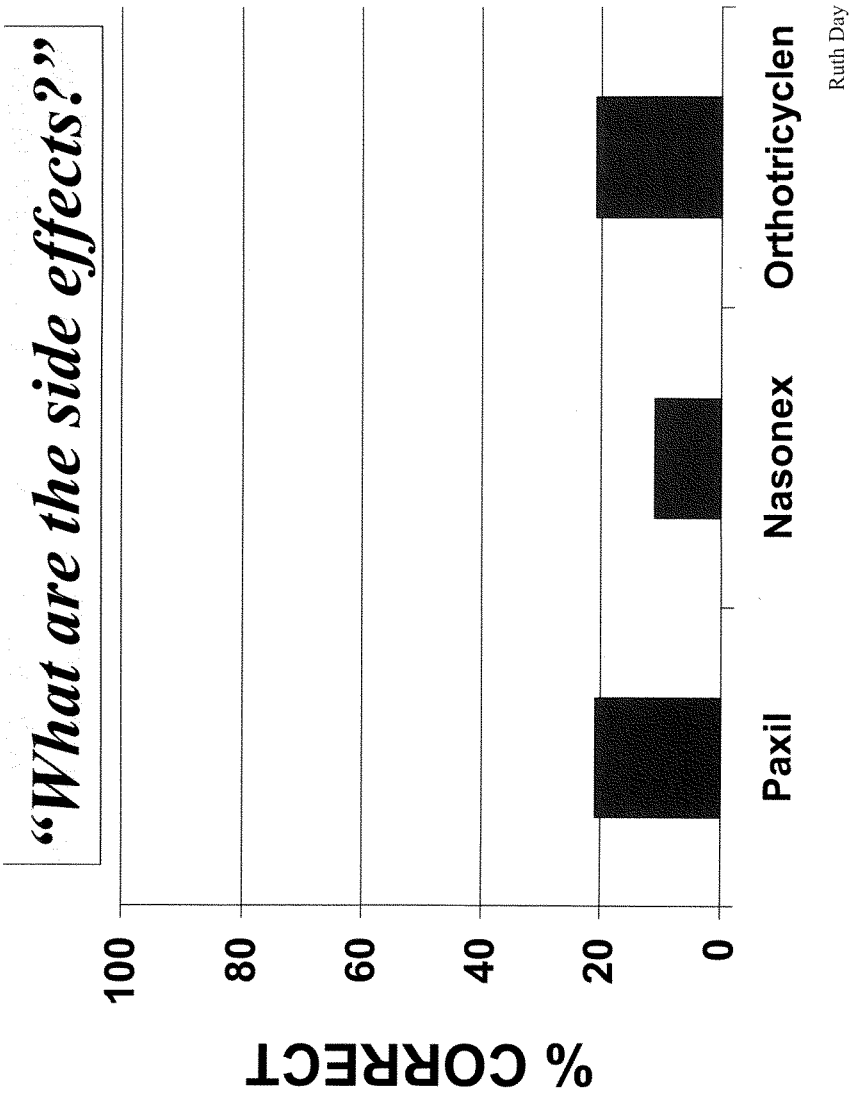
Study them all

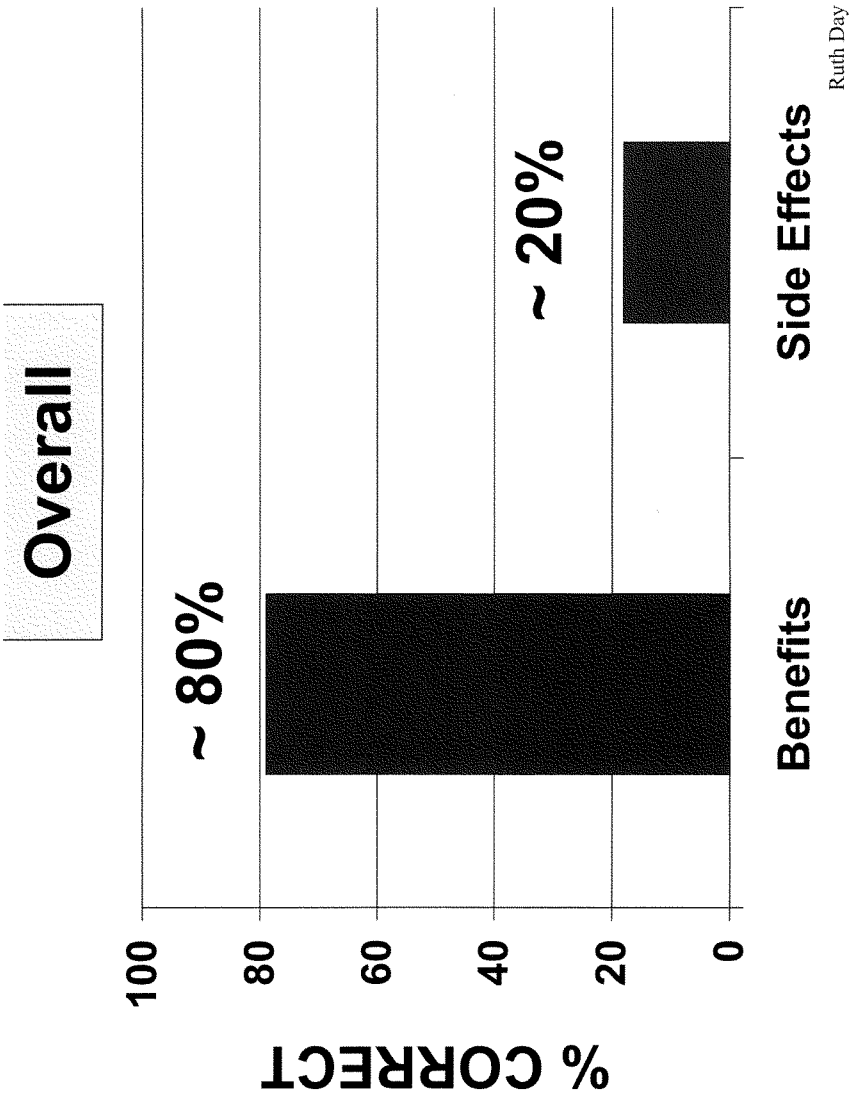
Experiments
Ruth Day

Experiments




"What is it for?"
% CORRECT
100
80
60
40
20
0
Paxil
Nasonex
Orthotricyclen
Ruth Day

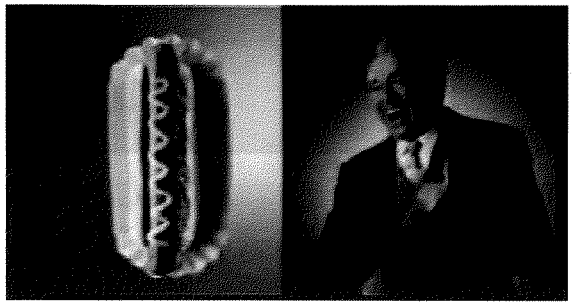

"What are the side effects?"
% CORRECT
100
80
60
40
20
0
Paxil
Nasonex
Orthotricyclen
Ruth Day


Overall
~ 80%
~ 20%
% CORRECT
100
80
60
40
20
0
Benefits
Side Effects
Ruth Day

Vytorin

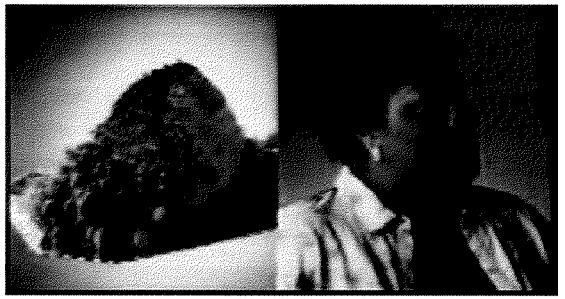
2 Sources of Cholesterol

Food & Family



Foot-long Frank

Your Grandpa Frank



Virginia Ham

Aunt Ginny

Wellbutrin-XL

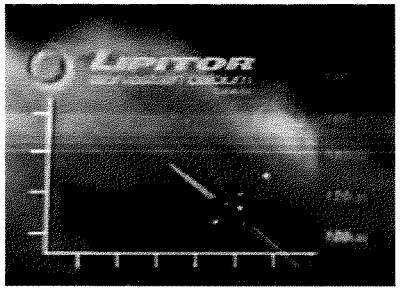




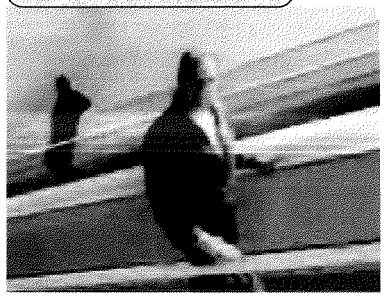
Treats depression

Low risk of sexual side effects

Benefits



Lipitor

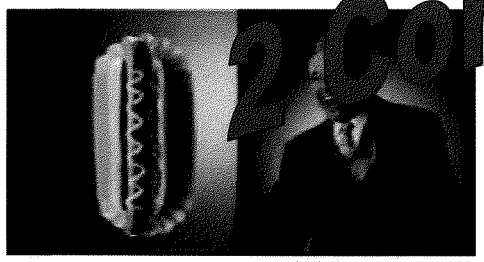


Crestor



Caduet

2 Concepts



Vytorin



Wellbutrin

Why Know About Risks?

Quote

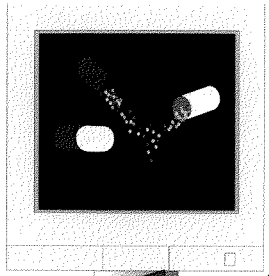
"Drug [information] should be [provided] only in such medical terms as are not likely to be understood by the ordinary individual."

--*Federal Register*, 1938
U.S. Regulations

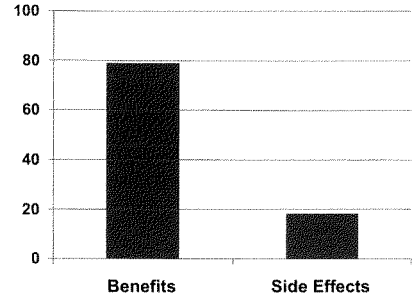
Why Know About Risks?

Today

Pros	Cons
1) Informed consent	1) Scare people
2) Decision making	2) They cannot understand
3) Take appropriate actions	3) They won't comply



Why hard?



Many possible reasons

--fear
--motivation
--education
--health literacy
--etc.

Rx TV Ads
Transcript
--Benefits
--Risks
--etc.
Rx
Ruth Day

Language Level

Many linguistic measures

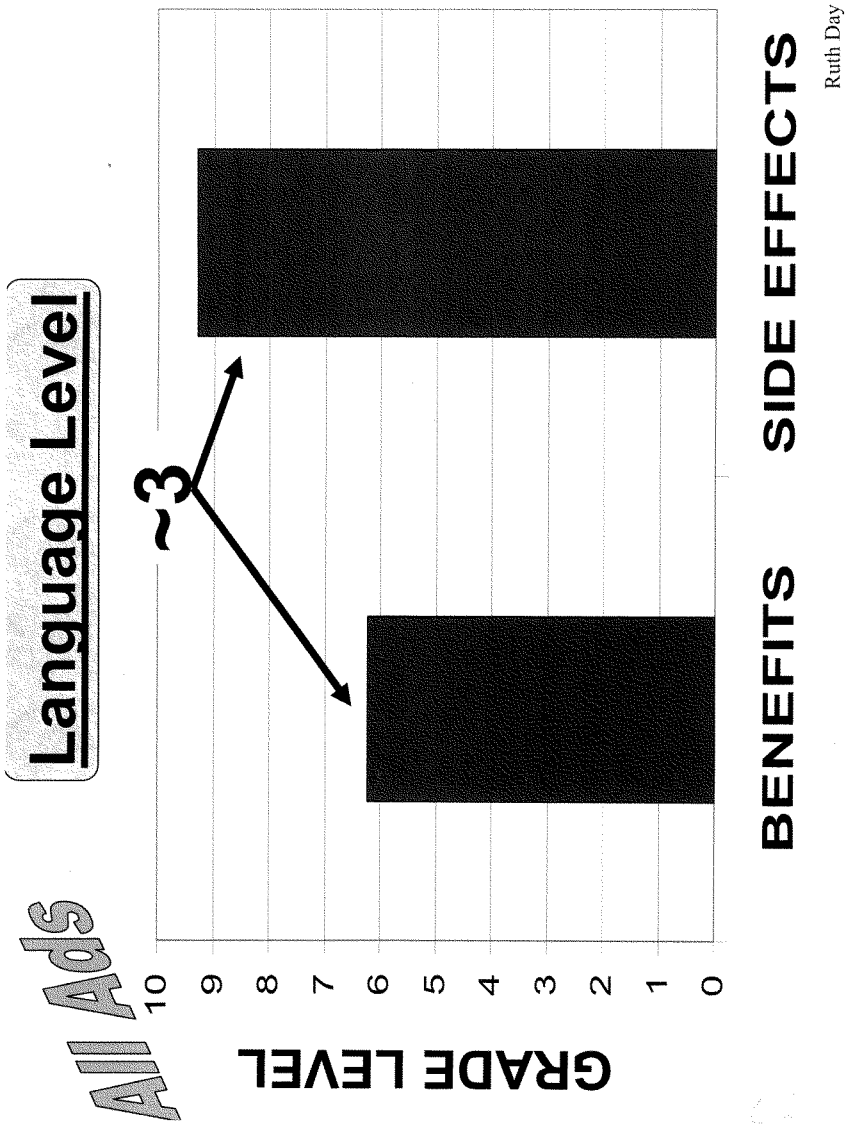
--word selection
--grammatical structure
--logical structure
--cohesion
--"readability"
--etc.

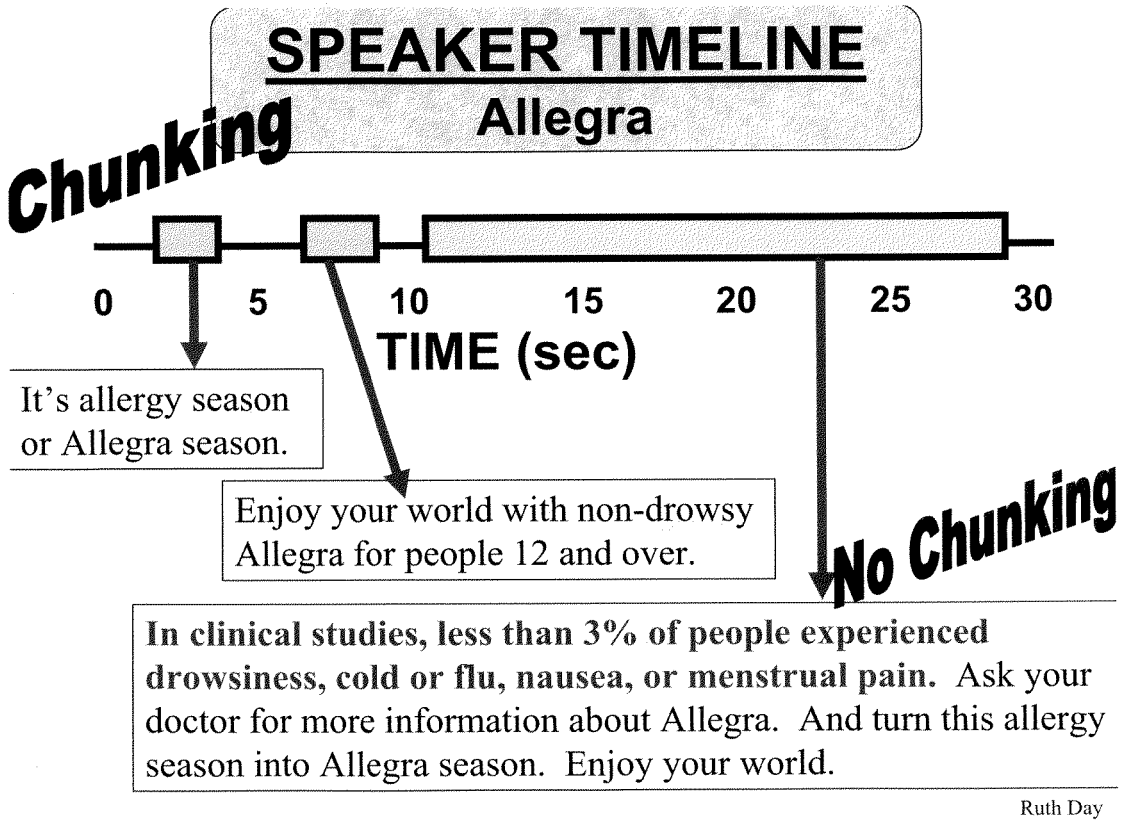
} **comprehension**

2001 Rx Drug Ads

Allegra	Lipitor	Remicade
Ambien	Meridia	Serevent
Celebrex	Nasonex	Singulair
Claritin	Orthotricyclen	Sonata
Denavir	Patanol	Tamiflu
Diflucan	Paxil	Valtrex
Flonase	Pravachol	Vioxx
Flovent	Prevacid	Wellbutrin SR
Imitrex	Prilosec	Zyrtec
Lamisil	Procrit	

Ruth Day

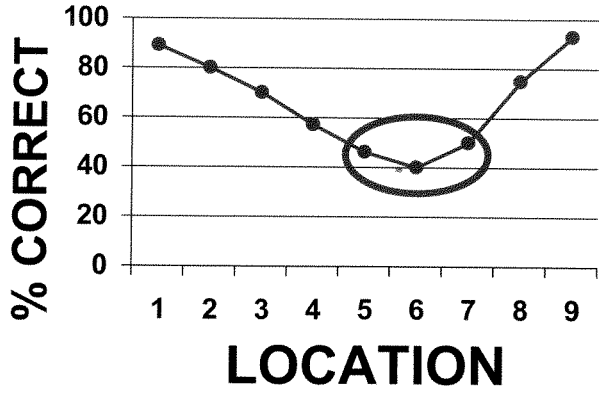

All Ads
Language Level
~3
GRADE LEVEL
10
9
8
7
6
5
4
3
2
1
0
BENEFITS
SIDE EFFECTS
Ruth Day


SPEAKER TIMELINE
Allegra
Chunking
0
5
10
15
20
25
30
TIME (sec)
It's allergy season or Allegra season.
Enjoy your world with non-drowsy Allegra for people 12 and over.
No Chunking
In clinical studies, less than 3% of people experienced drowsiness, cold or flu, nausea, or menstrual pain. Ask your doctor for more information about Allegra. And turn this allergy season into Allegra season. Enjoy your world.
Ruth Day

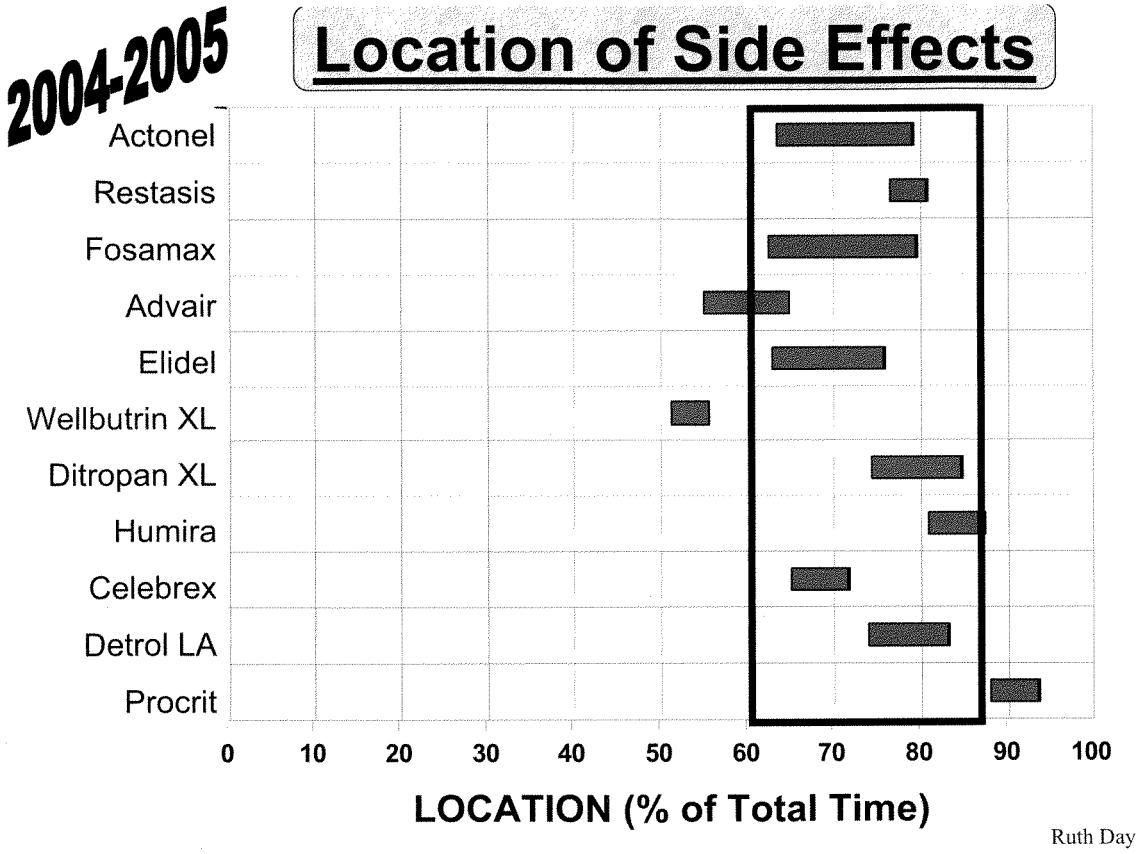
Well-Known Phenomenon

Task: --see/hear list of items
--report them

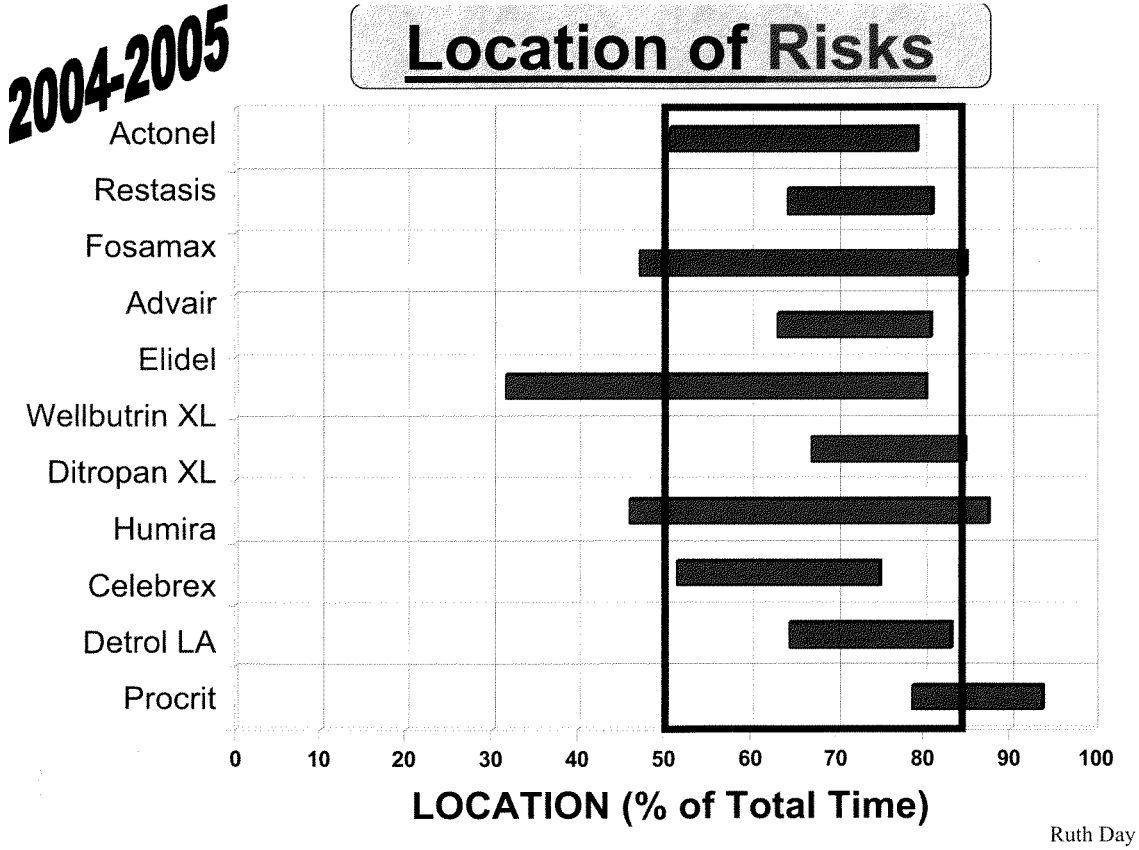
Typical Results:



Ruth Day


2004-2005
Location of Side Effects
Actonel
Restasis
Fosamax
Advair
Elidel
Wellbutrin XL
Ditropan XL
Humira
Celebrex
Detrol LA
Procrit
0
10
20
30
40
50
60
70
80
90
100
LOCATION (% of Total Time)

Ruth Day


2004-2005
Location of Risks
Actonel
Restasis
Fosamax
Advair
Elidel
Wellbutrin XL
Ditropan XL
Humira
Celebrex
Detrol LA
Procrit
0
10
20
30
40
50
60
70
80
90
100
LOCATION (% of Total Time)

Ruth Day

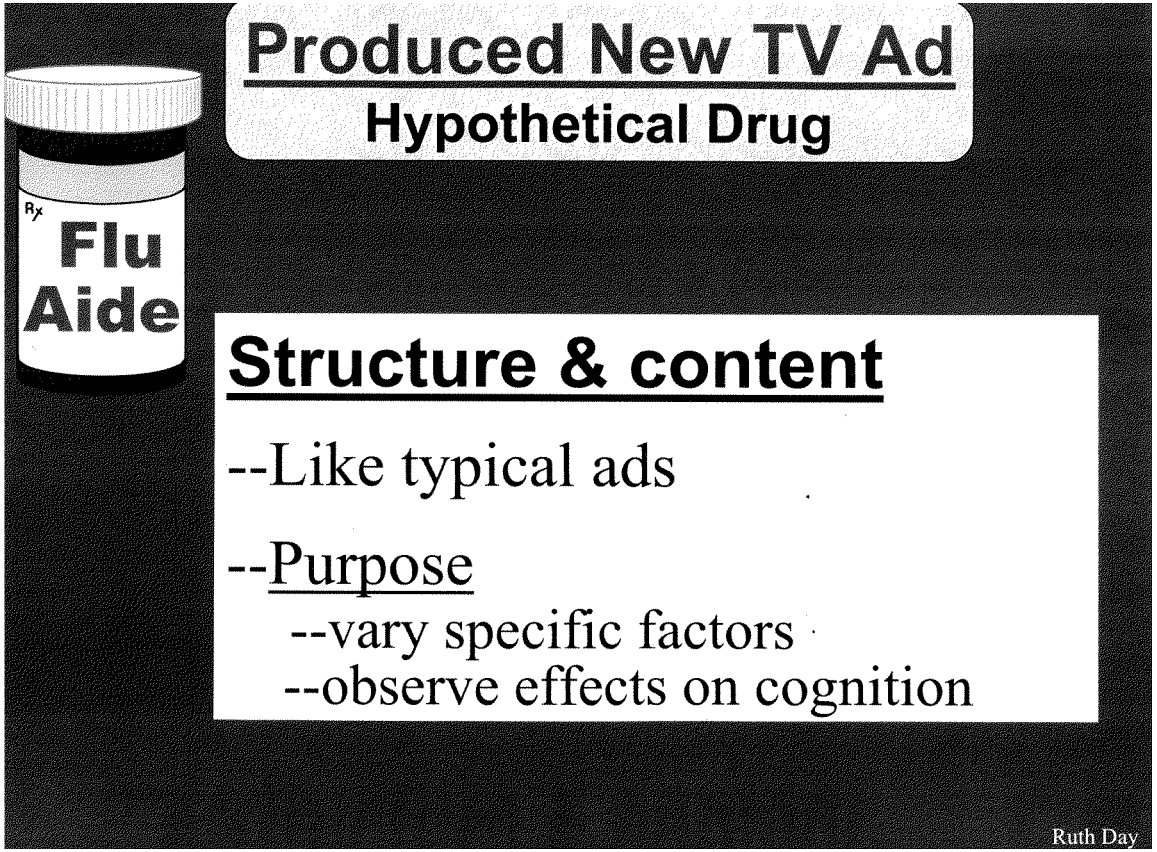
Location of Risks

Unfavorable!

But

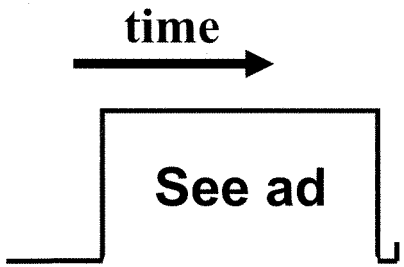
--What effect does location have on cognition?

--Need evidence


Produced New TV Ad
Hypothetical Drug
Rx
Flu
Aide
Structure & content
--Like typical ads
--Purpose
--vary specific factors
--observe effects on cognition
Ruth Day



Experiment



LOCATION
of Side Effects

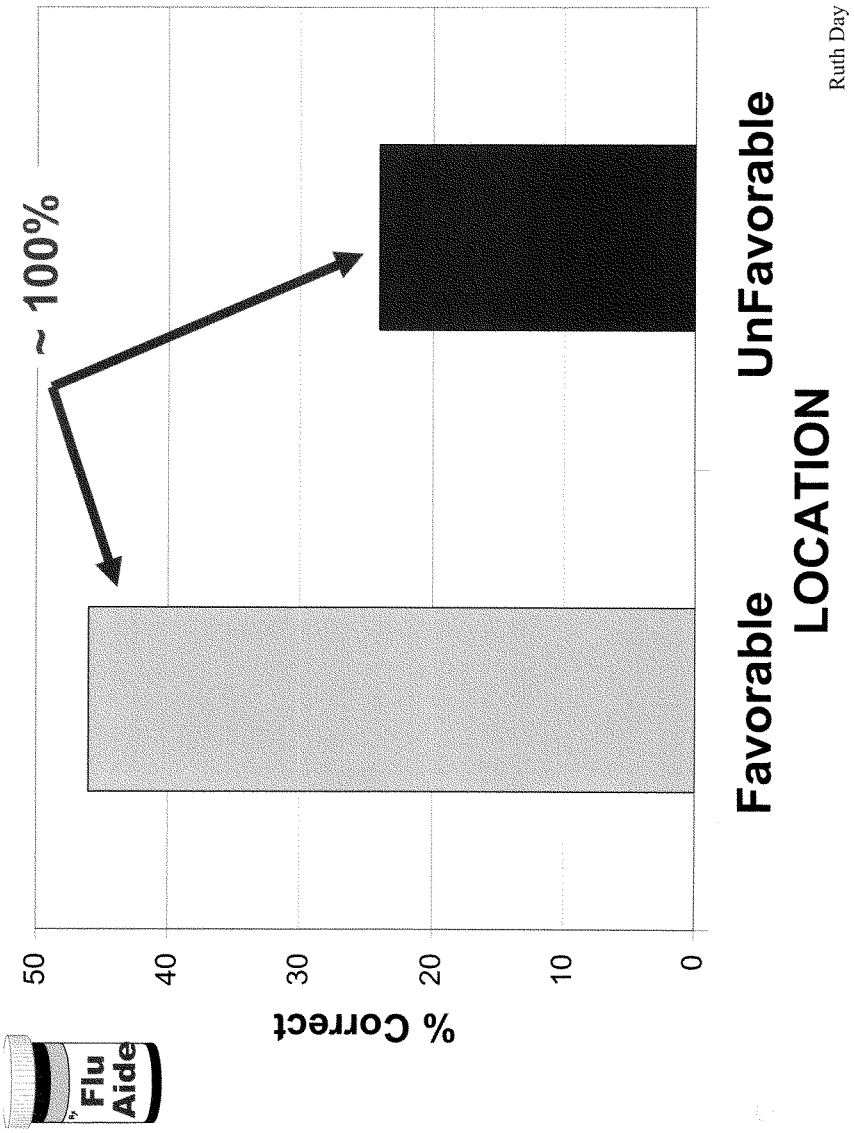
OR

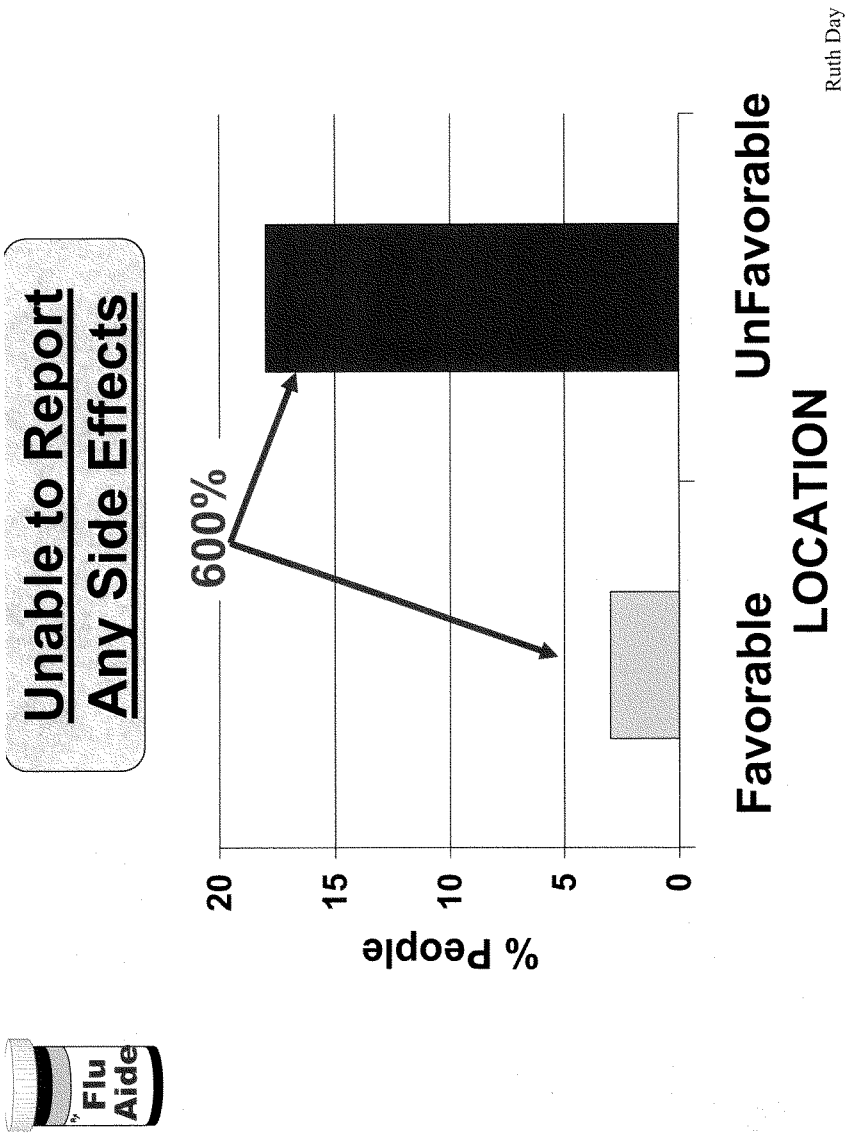
Favorable UnFavorable

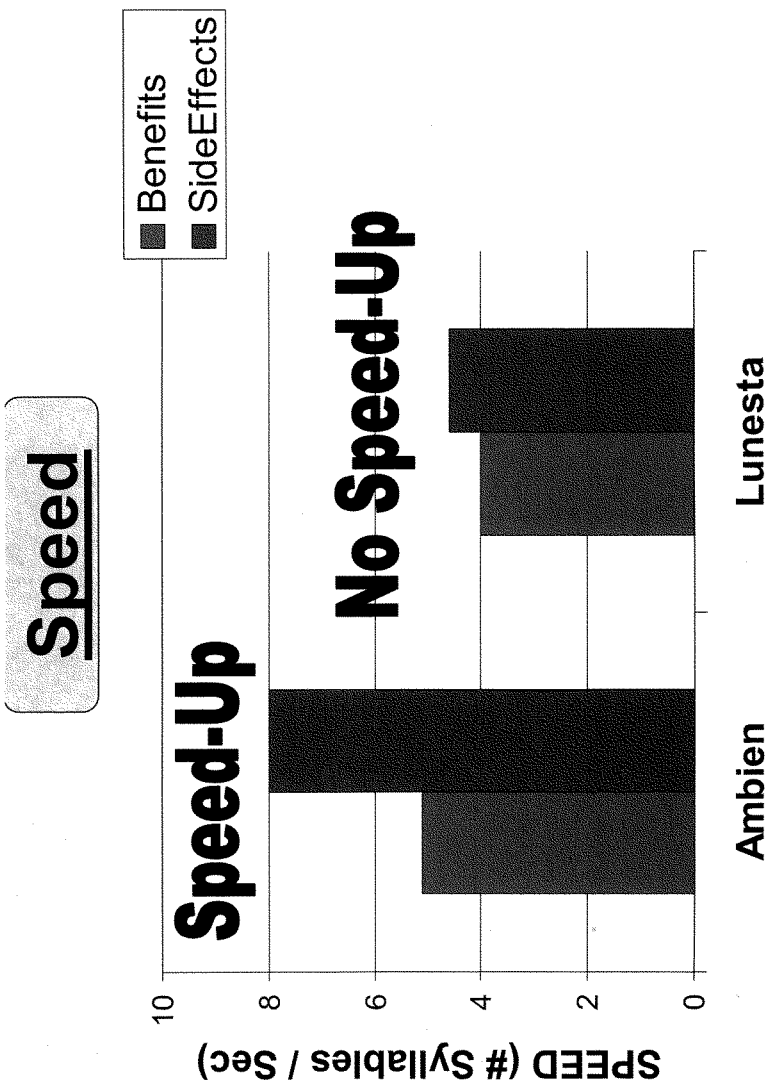
Same visual
Same auditory

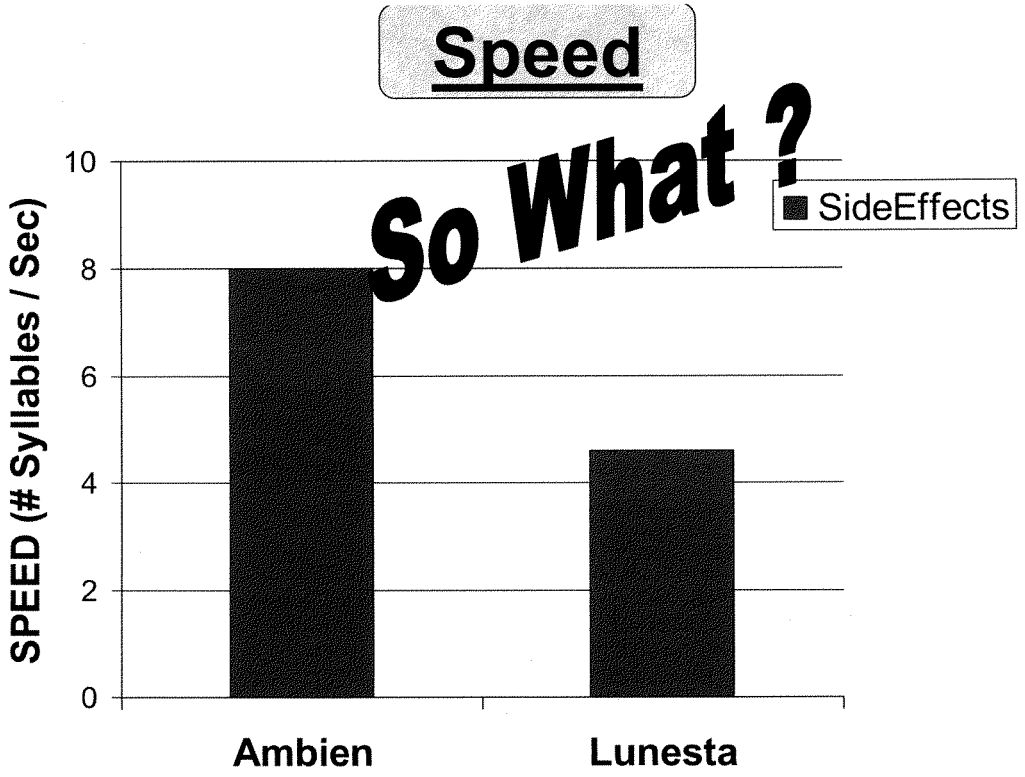
Differ only in location of side effects

Ruth Day

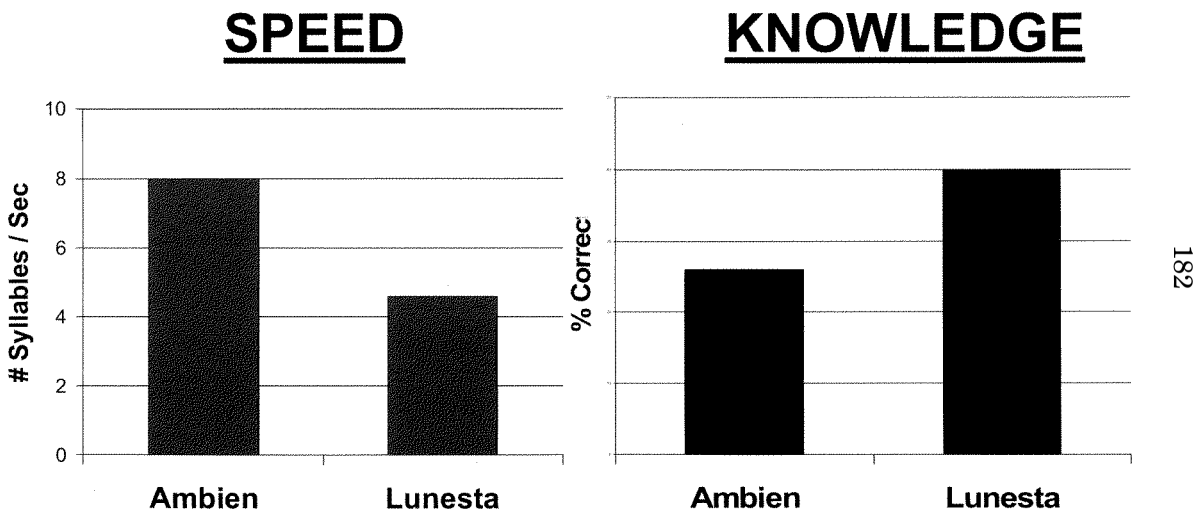

~ 100%
% Correct
50
40
30
20
10
0
Favorable
UnFavorable
LOCATION
Flu Aide
Ruth Day


Unable to Report
Any Side Effects
600%
20
15
10
5
0
% People
Favorable
UnFavorable
LOCATION
Flu
Aide
Ruth Day


Speed
Benefits
SideEffects
Speed-Up
No Speed-Up
SPEED (# Syllables / Sec)
10
8
6
4
2
0
Ambien
Lunesta


Speed
So What ?
SideEffects
SPEED (# Syllables / Sec)
10
8
6
4
2
0
Ambien
Lunesta

Speed



Ruth Day

Attention
Ruth Day

2005

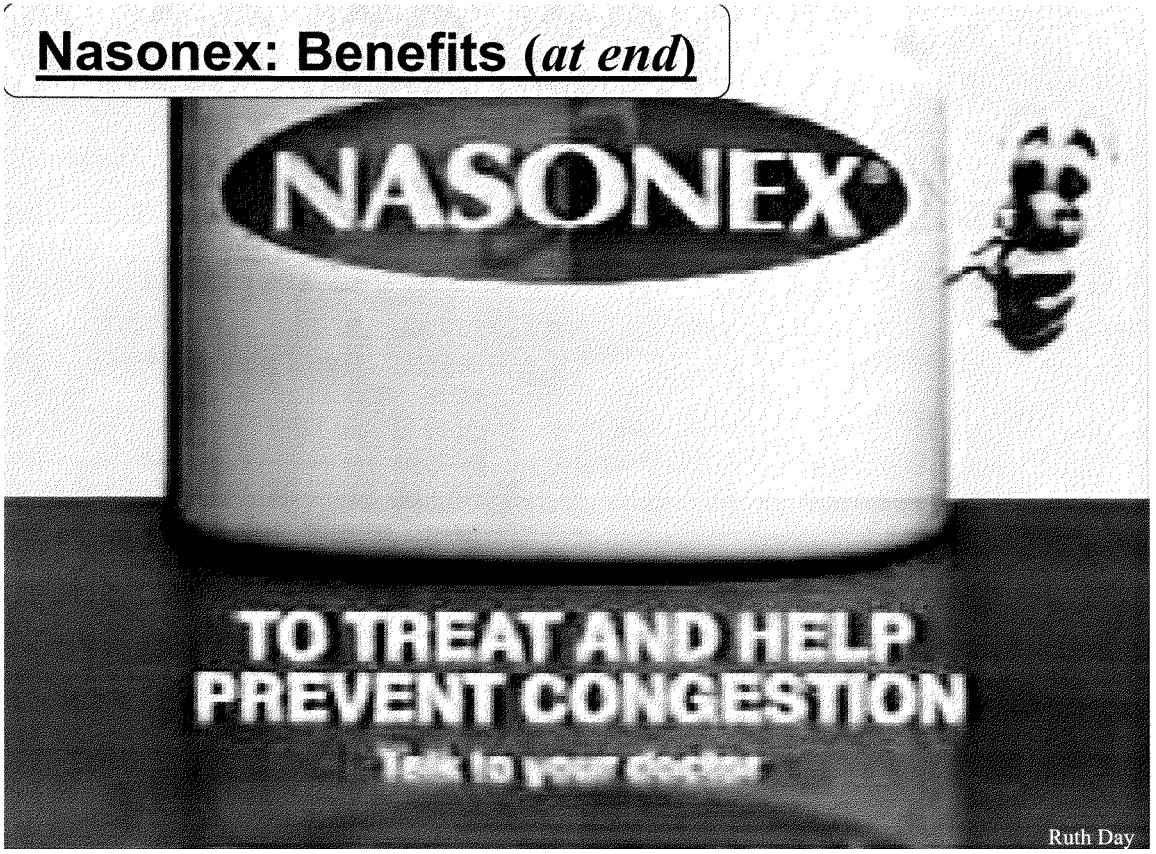
Nasonex

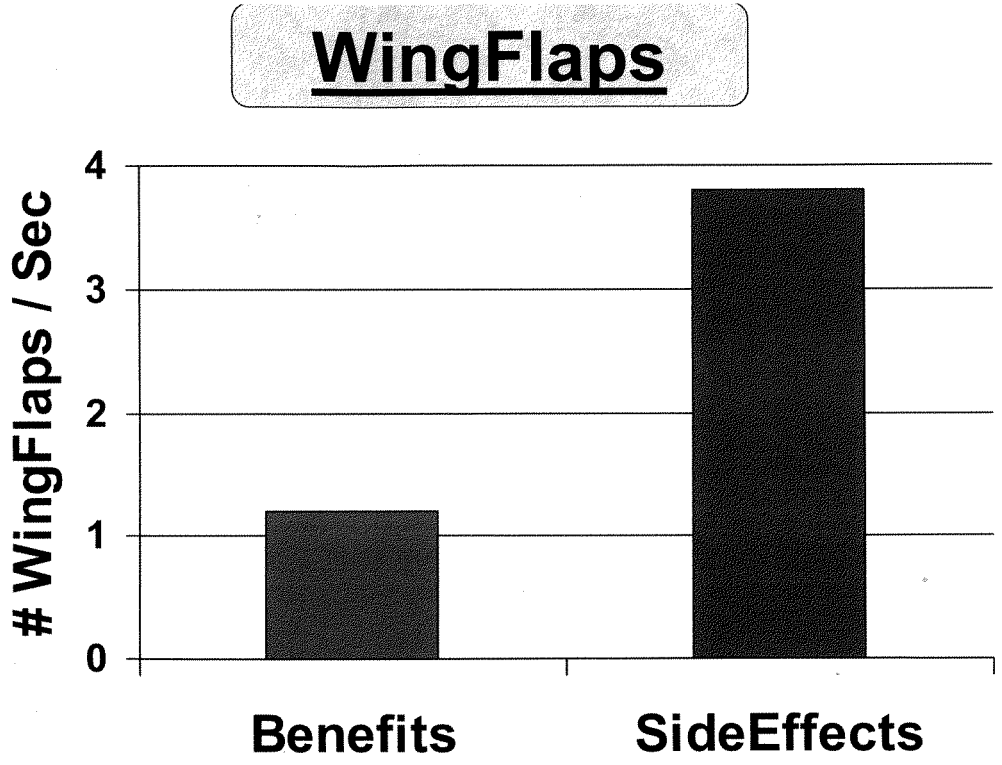


Ruth Day

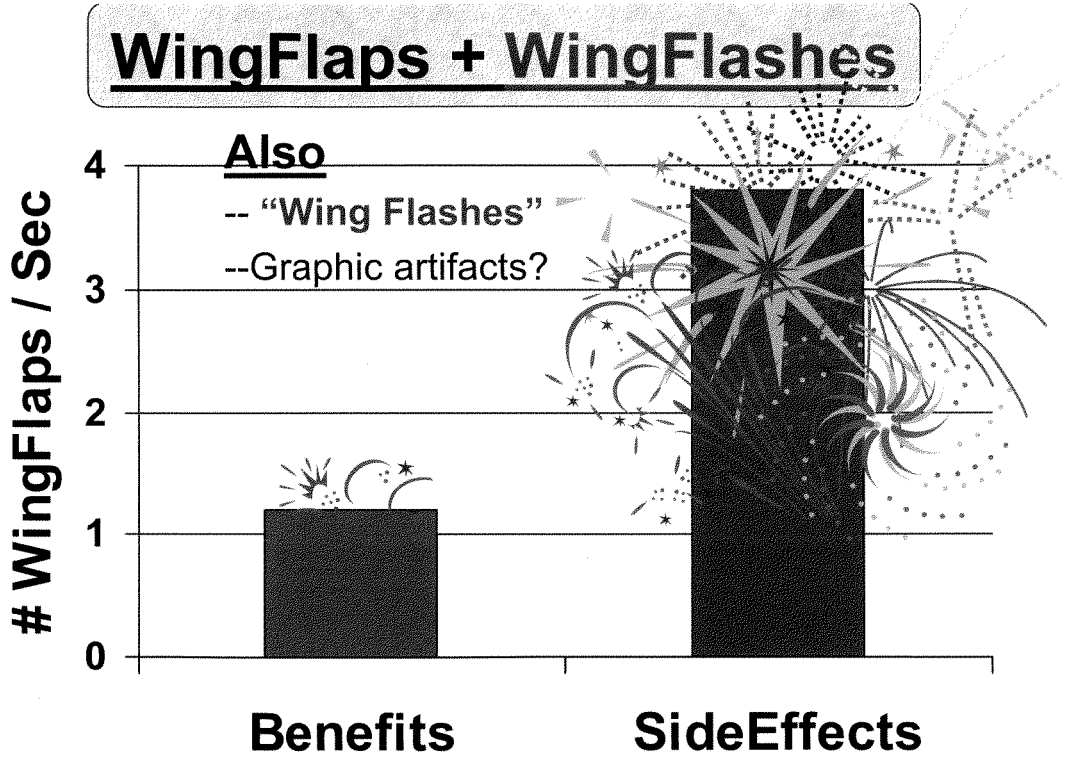
Nasonex: Side Effects

Nasonex: Benefits (*at end*)





Ruth Day


WingFlaps + WingFlashes
Also
-- "Wing Flashes"
--Graphic artifacts?
WingFlaps / Sec
4
3
2
1
0
Benefits
SideEffects

Ruth Day

Nasonex



--WingFlaps
--WingFlashes
--Sparkly

1) Divided attention

2) Decreased knowledge

3) Comments

"There weren't any side effects."

Nasonex



2005 → **2006**

First reported at

FDA Public Meeting on DTC (11/05)

Original



Flashing white wings

Subsequent Versions



Soft black wings

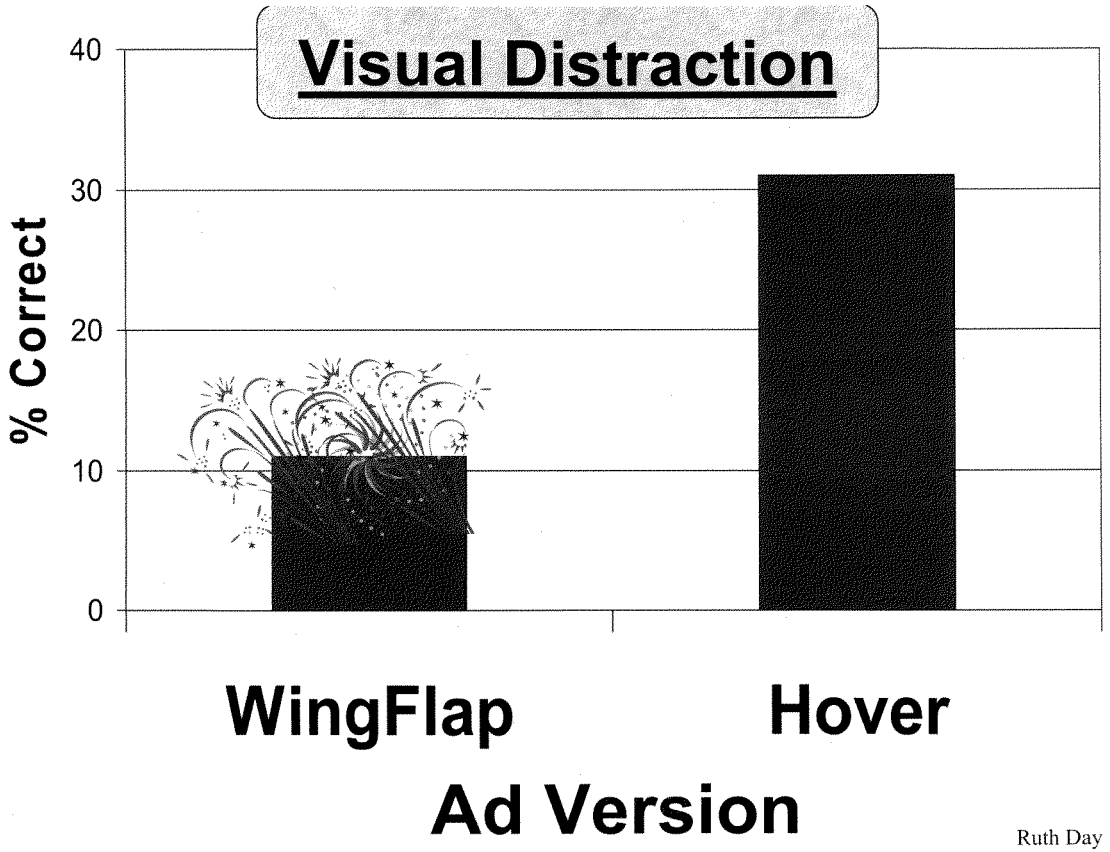


~ No wings / Hover



No bee

Ruth Day


Visual Distraction
40
30
20
10
0
% Correct
WingFlap
Hover
Ad Version

Ruth Day



Why hard?

Factors

- --Language level
- --Chunking
- --Location
- --Speed
- --Visual Distraction
- --*etc*.....

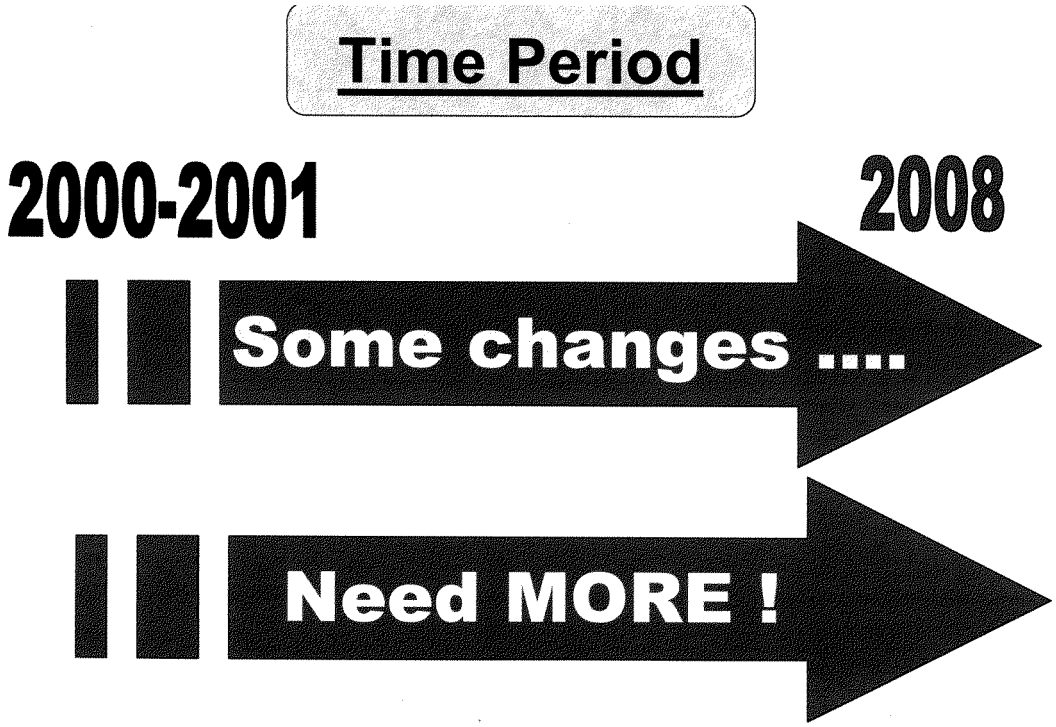
Conclusions
Ruth Day

Current Practices

Unfair Balance



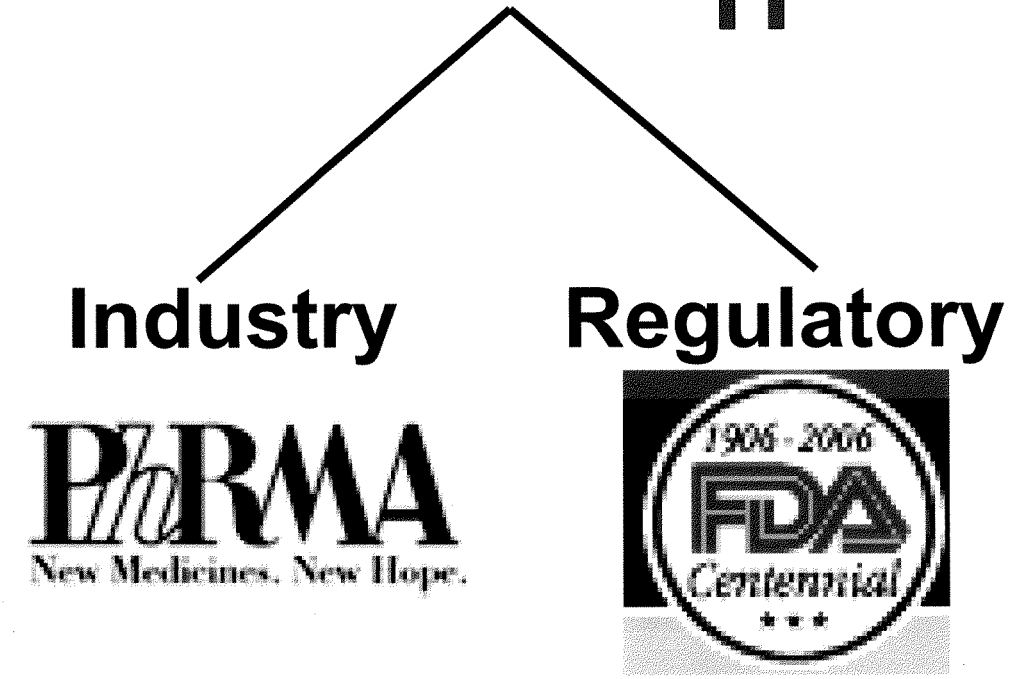
Cognitive Accessibility


Time Period
2000-2001
2008
Some changes ....
Need MORE !

RISK INFORMATION
Physically present
Functionally absent

Recommendations
Ruth Day

Evidence-based Approach

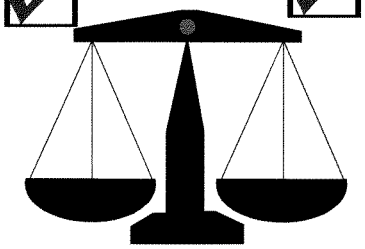


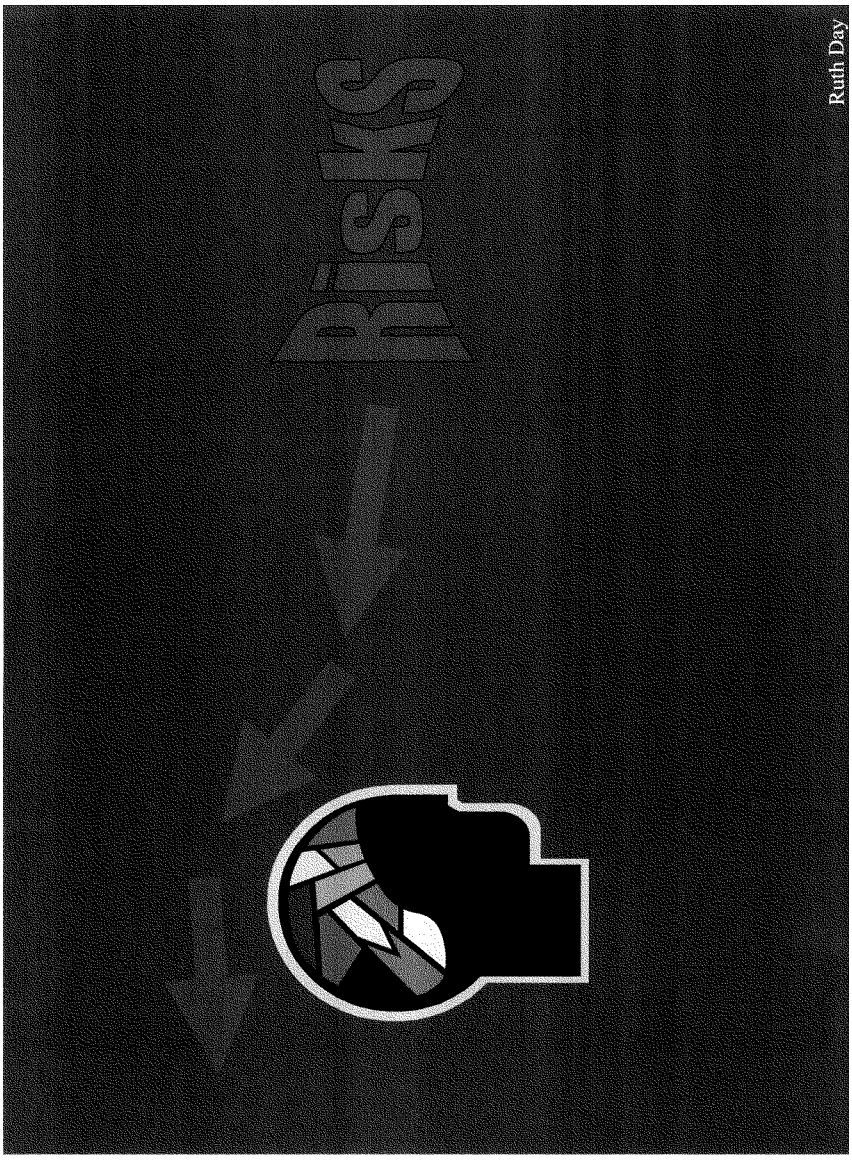
Ruth Day

Evidence-based Approach

Cognitive Accessibility

	Benefits	Risks
Location	☑	☑
Speed	☑	☑
Competing information	☑	☑
(etc.)		




SKIES
Ruth Day

Cognitive Accessibility
Ruth Day

DTC Drug Ads:

What Do People Understand & Remember?

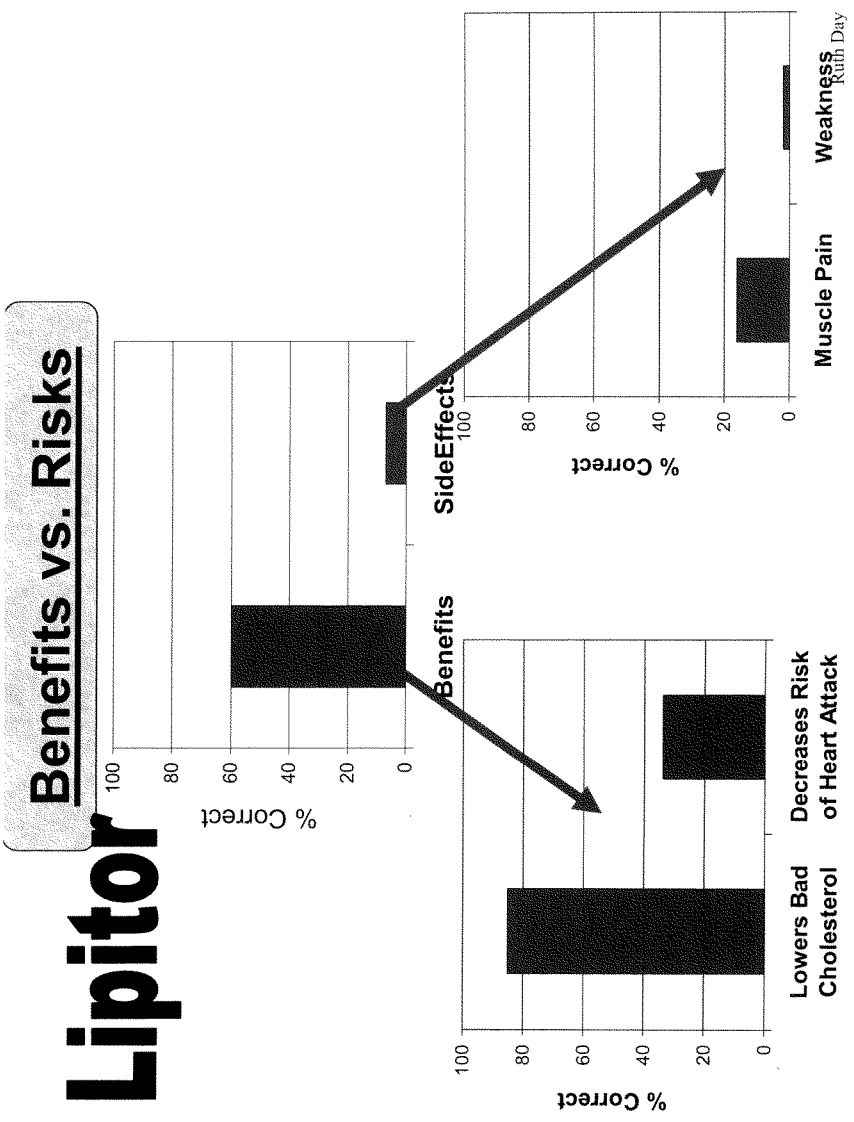


ruthday@duke.edu

http://www.duke.edu/~ruthday/medcog.html

Day, R.S. (2006) Comprehension of prescription drug information: Overview of a research program. ***Proceedings of the American Association for Artificial Intelligence, Argumentation for Consumer Healthcare.***

House Request
Examine Ads for Hearing
Ruth Day

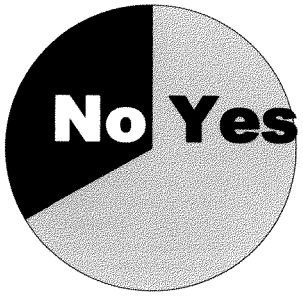

Lipitor
Benefits vs. Risks
% Correct
100
80
60
40
20
0
Benefits
Lowers Bad Cholesterol
Decreases Risk of Heart Attack
SideEffects
Muscle Pain
Weakness
Ruth Day

Lipitor

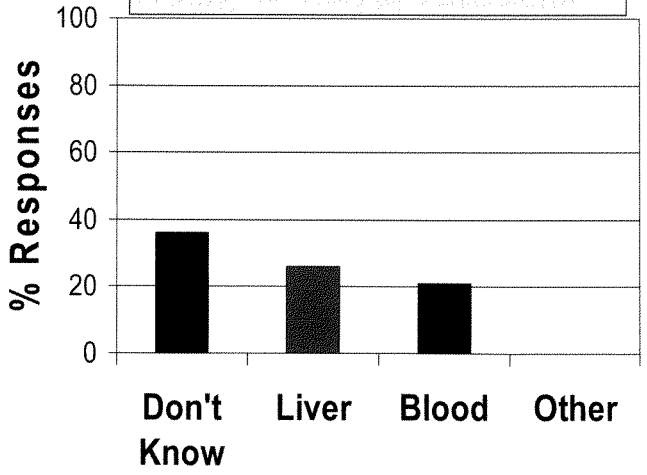
Medical Tests

"You need simple blood tests to check for liver problems."

"Are any medical tests needed?



"What medical test?



Ruth Day

Lipitor

Medical Tests

"You need simple blood tests to check for liver problems."

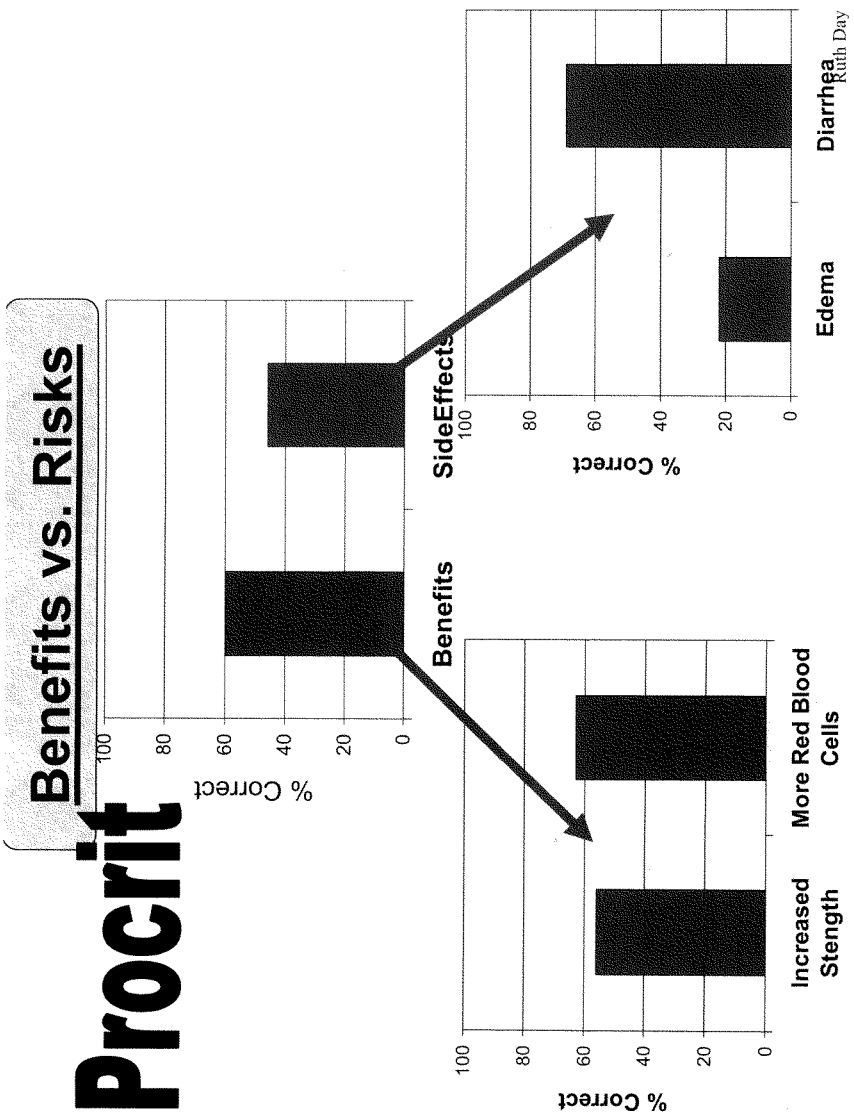
"When should this test be done?

--before taking..... 85%

--when you're old

--middle age

--(etc.)


Procrit
Benefits vs. Risks
% Correct
100
80
60
40
20
0
Benefits
Increased Stength
More Red Blood Cells
SideEffects
Edema
Diarrhea
Kath Day

DTC Drug Ads:

What Do People Understand & Remember?



ruthday@duke.edu

http://www.duke.edu/~ruthday/medcog.html

#	Description	Date
	Lipitor - Pfizer Documents	
1	Lipitor Advertisement Screenshot-Dr. Robert Jarvick	
2	Pfizer-Lipitor Advertisements Screenshots and Scripts	
3	Pfizer, Inc Endoresement Agreement with Dr. Robert Jarvick	04/13/2006
4	Talent Partners Invoice and production notes, re: Dennis Williams, performer.	03/27/2006
5	Talent Partners Invoice and production notes, re: Dennis Younglove, performer.	11/08/2007
6	Letter to Jeffrey Kindler, Pfizer CEO, from Utah Artificial Heart Institute.	08/10/2006
7	Pfizer Response Letter to Dr. Don Olsen of the Utah Artificial Heart Institute.	08/28/2006
8	ABC News Transcript from "Good Morning America." Interview with Dr. Robert Jarvick	01/16/2008
9	Declaration of Use of Lipitor by Dr. Robert Jarvick.	06/22/2006
10	Maya Group Report, "Pfizer Jarvick Advertising Campaign Diagnostic Research."	Nov. 2006
11	Mindy Goldberg Associates, Inc. report, "Lipitor Generic Defense Consumer Qualitative Research."	02/01/2007
12	Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use.	07/07/2006
13	American Medical Association Policy, H-105.988, "Direct-to-Consumer Advertising of Prescription Drugs and Implantable Devices."	
14	Email correspondence from Wayne Amchin, FDA DDMAC Project Manager, re: "Lipitor DTC User Fee Submissions..."	12/31/2007
15	"Vendor List"	
16	Letter from Pfizer Senior VP Anthony Principi to Chairmen Dingell and Stupak, re: Lipitor Advertisements.	02/25/2008
	Vytorin - Merck/Schering-Plough Documents	
17	Vytorin Advertisement Screenshot	
18	Vytorin Advertisements Screenshots and Scripts.	
19	Vytorin Print Advertisements	
20	Aboutyourcholesterol.com. "The Complete Site to Controlling High Cholesterol and Maintaining Good Heart Health."	
21	Email correspondence from Mark Askine, re: "Vytorin Promotional Materials."	01/16/2008
22	Email correspondence from Eric DeGroot of Imagepace, re: "Batch Reading Discrepancies."	03/15/2006
23	Email correspondence from Eric DeGroot, re: "SP Efficacy Analysis QC."	08/23/2006
24	Email correspondence from Professor John Kastelein, of University of Amsterdam.	12/12/2006

25	Schering Plough ENHANCE Consultancy Report by Michiel Bots of University Medical Center Utrecht.	01/26/2007
26	Email correspondence from Alice Bova, Scherign Plough Research Institute, re: "ENHANCE and the Decision Today."	06/18/2007
27	Email correspondence from Thomas Musliner, re: ENHANCE - Confidential."	07/09/2007
28	Email correspondence from Enrico Veltri of Schering Plough, re: "ENHANCE."	07/17/2007
29	Email correspondence from Thomas Musliner to Briggs Morrison, et al, re: "Can either of you join?"	08/08/2007
30	Email Correspondence from Elizabeth Stoner to Briggs Morrison, et al, re: "Thank you."	08/21/2007
34	Email correspondence from John Strony to Toni Bransford, et al, re: "ENHANCE."	08/22/2006
32	Email Correspondence from Enrico Veltri to Sean McNicholas, et al, re: "ENHANCE - status."	09/17/2007
	Procrit - Ortho Biotech Documents	
33	Procrit Advertisement Screenshot	
34	Ortho Biotech Procrit Advertisements Screenshots and Scripts	
35	Procrit– Chronology of FDA Regulation of ESA "Quality of Life" Advertising	
36	Letter from FDA Center for Biologics Evaluation and Research (CBER) to Amgen/J&J, re: denying application for "quality of life" indication.	09/17/1996
37	Letter from FDA CBER to Amgen/J&J, re: denying application for "quality of life" indication.	03/02/1998
38	Letter from Amgen/J&J to FDA Advertising and Promotional Labeling Branch (APLB), CBER, re: proposed Procrit "quality of life" advertisement.	10/28/1998
39	Letter from William Purvis of FDA APLB to Ralph Smalling of Amgen/J&J.	11/06/1998
40	Letter from Amgen/J&J to FDA APLB	11/20/1998
41	Letter from FDA APLB to Amgen, re: complaint about off-label promotion of Procrit at higher levels than indicated.	03/30/1999
42	Letter from FDA APLB to Amgen, re: another complaint about off-label promotion of Procrit at higher levels than indicated.	05/11/1999
43	Letter from Amgen/J&J to FDA CBER, re: renewed application for "fatigue" indication.	01/24/2000
44	Letter from FDA APLB to Amgen/J&J, re: multi-element promotional campaign for Procrit.	06/30/2000
45	Letter from Amgen/J&J responding to 6/30/00 letter from FDA APLB.	08/09/2000
46	Letter from Amgen/J&J referring to 7/21/00 teleconference regarding 6/30/00 letter from FDA APLB.	08/16/2000
47	Letter from Amgen/J&J to FDA APLB concerning FDA 6/30/00 letter.	08/23/2000
48	Letter from Amgen/J&J to FDA CBER documenting FDA "willingness to change the position that was set forth in your June 30, 2000 letter…"	01/05/2001

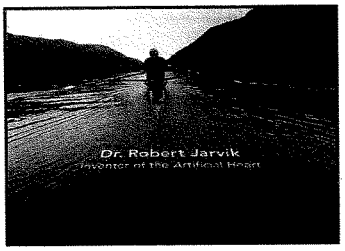
49	Letter from Amgen/J&J to FDA stating intention to renew application for "quality of life" indication for cancer patients.	05/18/2001
50	Letter from FDA APLB to Amgen/J&J, re: "false and misleading" aspects of Procrit advertising, including two DTC broadcast (TV) ads ("Anthem" and "Big Boy Bed") and requesting J&J revise advertising materials accordingly.	12/21/2001
51	Handwritten notes of OCC meeting regarding FDA 12/21/01 letter.	01/10/2002
52	Letter from Amgen/J&J responding to FDA 12/21/01 letter.	01/25/2002
53	Letter from Amgen/J&J responding to FDA 12/21/01 letter.	02/12/2002
54	FDA CBER Review Memorandum, re: Amgen/J&J response letter to CBER's 12/21/01 l letter.	April 2002
55	Email correspondence within FDA from Broadnax to Byrd and Abrams regarding teleconference following day to address OCC viewpoint of Procrit advertising issues contained in FDA's 12/21/01 letter.	05/28/2002
56	Handwritten notes entitled "TC [Teleconference] w/ DDMAC re: Procrit."	05/29/2002
57	Letter from Amgen/J&J to FDA, re: proposed corrective actions to DTC broadcast (TV) ads.	05/10/2002
58	Letter from FDA to Amgen/J&J finding most of J&J's proposed corrective actions acceptable.	07/30/2002
59	Email correspondence from Dan Troy (former Chief Counsel, OCC) to Jeffrey Senger (OCC), re: J&J promotion of Procrit and related email chain.	02/27/2007
60	Email correspondence from Seth Ray to Sheldon Bradshaw and Mark Raza, re: draft EPO Q&A for Ways and Means.	06/20/2007
61	Article by Ruth Day, subject: "Comprehension of Prescription Drug Information: Overview of a Research Program."	2006
62	Report by GAO (GAO-07-54), subject: "Prescription Drug: Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising." (Summary and Index only, the full document can be found within the Subcommittee's files)	November 2006
63	Kaiser Foundation/ USA Today/ Harvard School of Public Health Report (Summary and Chartpack), subject: "The Public Prescription Drugs and Pharmaceutical Companies."	March 2008
64	PhRMA Guiding Principles, "Direct to Consumer Advertisements About Prescription Medicines."	November 2005
65	Institute of Medicine Report Brief, subject: "The Future of Drug Safety: Action Steps for Congress."	September 2006
66	The Guardian (UK publication) article by Sarah Boseley, subject: "EU Plan May Let Drug Firms Sidestep Ban on Advertising."	04/08/2008

LIPITOR

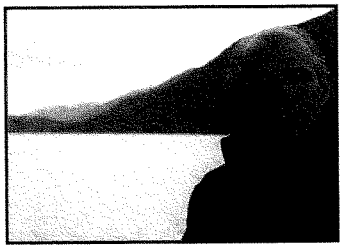
:60 Jarvik Revised (With Tag)
page 1 of 4

Pfizer - Lipitor
Campaign Name: "Jarvik"
Commercial Length: :60
LP272543B
ISCI: PFLI6016

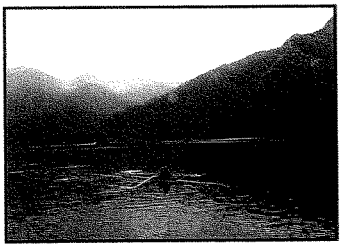
AVO: Dr. Robert Jarvik.
Inventor of the artificial heart.



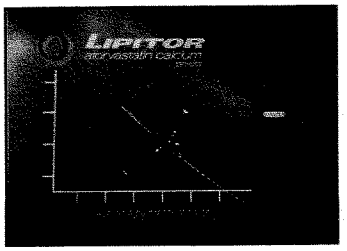
JARVIK V.O.: The average heart beats 2 billion times. The heart is amazing.



But high cholesterol can lead to heart disease.



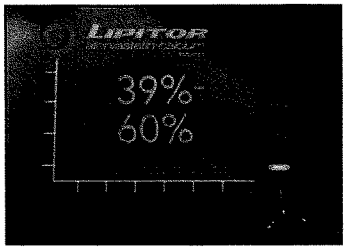
Lipitor can help. When diet and exercise aren't enough, adding Lipitor significantly...



KTG 000002

Pfizer - Lipitor
Campaign Name: "Jarvik"
Commercial Length: :60
LP272543B
ISCI: PFLI6016

...lowers bad cholesterol 39 - 60 %.



If you have several common risk factors for heart disease,



Lipitor is clinically proven to reduce your risk of heart attack.



And more cardiologists surveyed said they'd prescribe Lipitor for their own families than any other cholesterol lowering brand.



:60 Jarvik Revised (With Tag)
page 3 of 4

Lipitor is not for everyone, including people with liver problems...



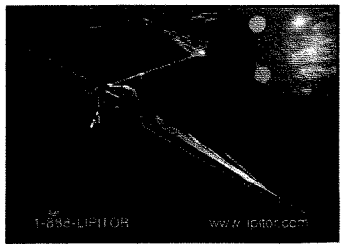
...and women who are nursing, pregnant or may become pregnant. You need simple blood tests to check for liver problems.



Tell your doctor if you are taking other medications or if you have any muscle pain or weakness. They may be a sign of a rare but serious side effect.



Lipitor is one of many treatment options to consider with your doctor.



KTG 000004

Pfizer - Lipitor
Campaign Name: "Jarvik"
Commercial Length: :60
LP272543B
ISCI: PFLI6016

It's your heart.



Ask if Lipitor is right for you.



V.O.: Visit Lipitor.com for a free trial.

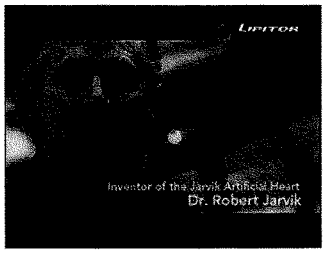


Pfizer-Lipitor
Human Body TV :60
PFLI-6296
LP276825
1 of 4

OPEN ON JARVIK IN FRONT OF AN HUGE, ADVANCED MOVING MODEL OF THE INSIDE OF A HUMAN BODY.

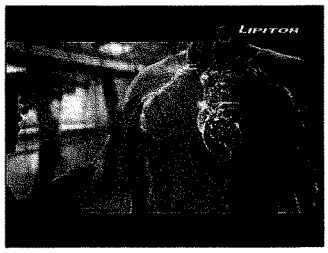


Dr. Jarvik:
In the human body the heart pumps blood through thousands of miles of arteries every minute.



AVO:
Inventor of the Jarvik Artificial Heart, Dr. Robert Jarvik.

HE USES A LASER TO POINT TO THE HEART



Jarvik:
But high cholesterol can clog arteries... and lead to heart disease...

AND THEN THE BRAIN



or a stroke.

Pfizer-Lipitor
Human Body TV :60
PFLI-6296
LP276825
2 of 4

CAMERA MOVES IN TOWARDS CHEST SHOWING HOW THE AMOUNT OF CHOLESTEROL HAS BEEN REDUCED.



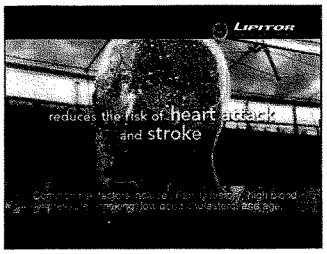
Adding Lipitor is proven to lower bad cholesterol an impressive 39 to 60% when diet and exercise are not enough.



And today, clinical evidence proves that Lipitor...



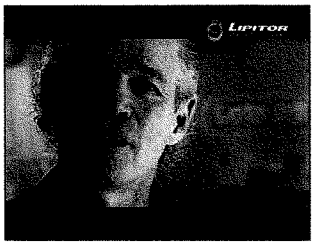
can reduce both your risk of heart attack...



and your risk of stroke... if you have several common risk factors for heart disease.

KTG 000007

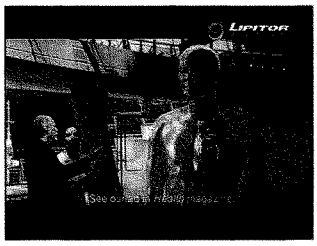
Pfizer-Lipitor
Human Body TV :60
PFLI-6296
LP276825
3 of 4



All important reasons to ask your doctor about Lipitor.



Lipitor is not for everyone, including people with liver problems and women who are nursing, pregnant or may become pregnant.



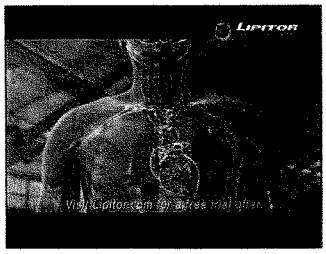
You need simple blood tests to check for liver problems.



Tell your doctor if you're taking other medications, or if you have any muscle pain or weakness. They may be a sign of a rare, but serious side effect.

KTG 000008

Pfizer-Lipitor
Human Body TV :60
PFLI-6296
LP276825
4 of 4



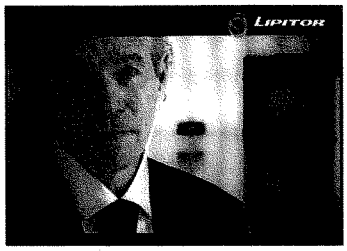
Lipitor is one of many treatment options to consider with your doctor.



Could you be doing more... with Lipitor? Ask your doctor.

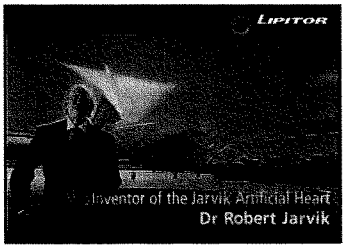
Pfizer/Lipitor
Podium with Free Trial and
New Jarvik Title :60 spot
ISCI: PFLI-6336
LP275716B
Page 1 of 3

the kaplan thaler group, ltd.
advertising & entertainment

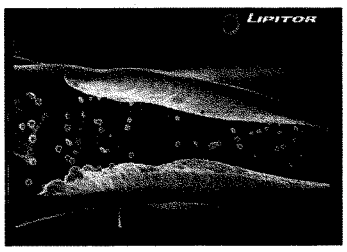


JARVIK: I've studied the human heart for a lifetime, and there's something you should know.

SUPER: Inventor of the Jarvik Artificial Heart Dr. Robert Jarvik

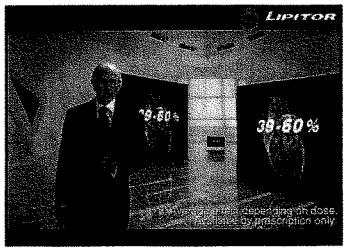


VO: Inventor of the Jarvik Artificial Heart, Dr. Robert Jarvik



JARVIK: High cholesterol can lead to heart disease.

SUPER: Average effect depending on dose. Available by prescription only.



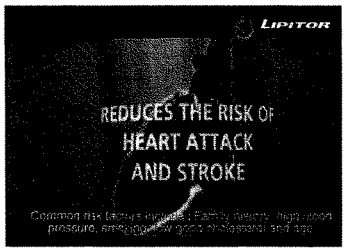
When diet and exercise aren't enough, adding Lipitor lowers bad cholesterol 39 to 60%.

KTG 000010

Pfizer/Lipitor
Podium with Free Trial and
New Jarvik Title :60 spot
ISCI: PFLI-6336
LP275716B
Page 2 of 3

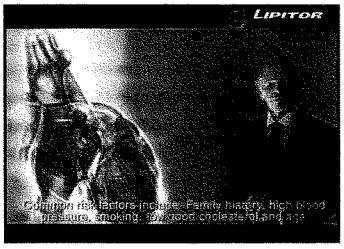
the kaplan thaler group, ltd.
advertising & entertainment

SUPER: Common risk factors include: Family history, high blood pressure, smoking, low good cholesterol and age.



And Lipitor is clinically proven to reduce your risk of heart attack... and... your risk of stroke... if you have several common risk factors for heart disease.

SUPER: Common risk factors include: Family history, high blood pressure, smoking, low good cholesterol and age.



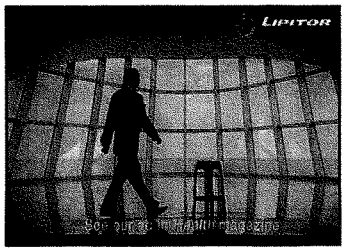
The more we learn about Lipitor, the more impressed I am.

SUPER: See our ad in *Health* magazine.



Lipitor is not for everyone, including people with liver problems and women who are nursing, pregnant or may become pregnant.

SUPER: See our ad in *Health* magazine.



You need simple blood tests to check for liver problems.

KTG 000011

Pfizer/Lipitor
Podium with Free Trial and
New Jarvik Title :60 spot
ISCI: PFLI-6336
LP275716B
Page 3 of 3

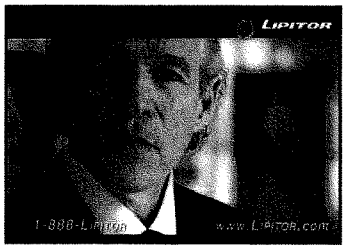
the kaplan thaler group, inc.
advertising & entertainment

SUPER: 1-888-LIPITOR
www.Lipitor.com

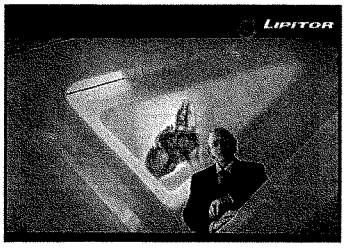


Tell your doctor if you're taking other medications, or if you have any muscle pain or weakness. They may be a sign of a rare, but serious side effect.

SUPER: 1-888-LIPITOR
www.Lipitor.com



Lipitor is one of many treatment options to consider with your doctor.



Could you be doing more... with Lipitor? Ask your doctor.

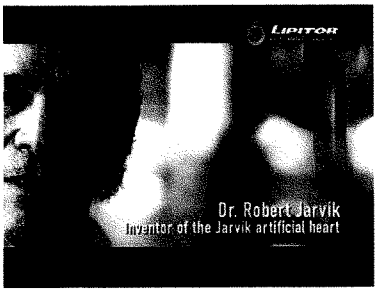
SUPER: free trial offer visit
www.Lipitor.com



VO: Visit Lipitor.com for a free trial.

KTG 000012

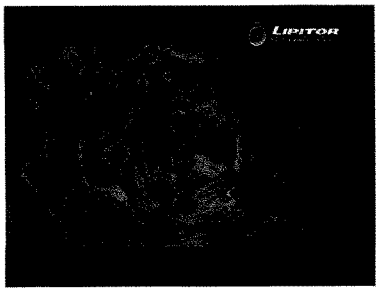
Pfizer - Lipitor
Stroke TV :60
PFLI7356
LPU00063E
1 of 4



AVO: Inventor of the Jarvik Artificial Heart, Doctor Robert Jarvik.

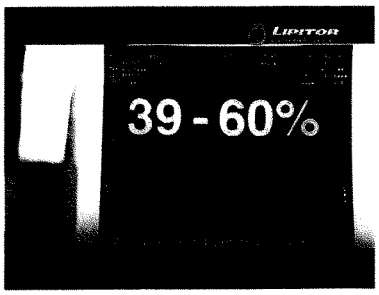
Super: Inventor of the Jarvik Artificial Heart, Doctor Robert Jarvik.

Dr. Jarvik: Heart disease and stroke are the first and third biggest health problems in America.



Dr. Jarvik: And high cholesterol can increase your risk of both.

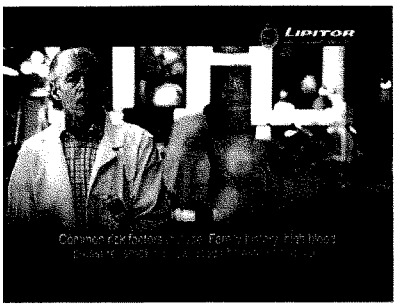
It can clog arteries anywhere. In the heart, it can lead to heart attack. In the brain, a stroke.



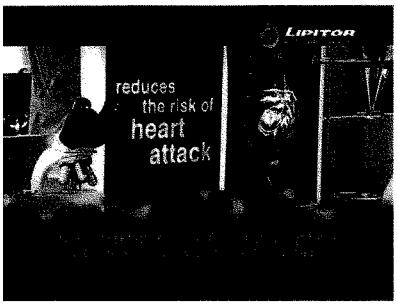
Adding Lipitor significantly lowers bad cholesterol 39-60%, when diet and exercise are not enough.

Super: Average effect depending on dose.

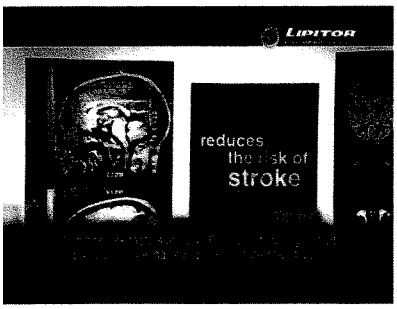
Pfizer - Lipitor
Stroke TV :60
PFLI7356
LPU00063E
2 of 4



And unlike some medicines,
Lipitor is FDA approved...



to reduce the risk of heart attack...



and stroke, if you have several common
risk factors for heart disease.

KTG 000014

Pfizer – Lipitor
Stroke TV :60
PFLI7356
LPU00063E
3 of 4



Dr. Jarvik: Impressive.



Lipitor is not for everyone, including people with liver problems and women who are nursing, pregnant or may become pregnant.

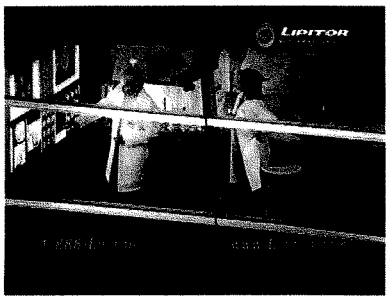
Super: See our ad in Health Magazine



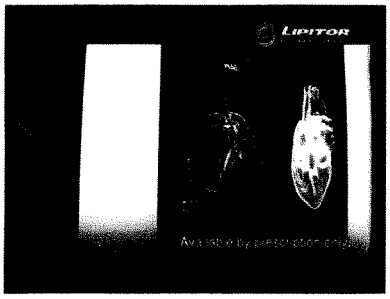
You need simple blood tests to check for liver problems.

Super: 1.888.LIPITOR
Super: www.lipitor.com

Pfizer - Lipitor
Stroke TV :60
PFLI7356
LPU00063E
4 of 4



Dr. Jarvik: Tell your doctor if you are taking other medications, or if you have any muscle pain or weakness. This may be a sign of a rare but serious side effect.



Lipitor is one of many treatment options to consider with your doctor.

Super: Available by prescription only.

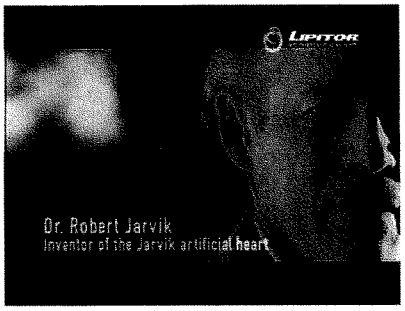


Dr. Jarvik: Lowering cholesterol is important. But could you be doing more...with Lipitor?

Ask your doctor. Don't wait.

KTG 000016

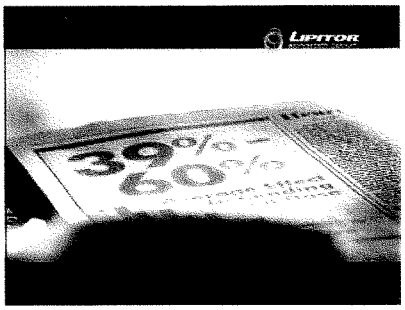
Lipitor – Pfizer
Breakfast TV :60
PFLI7016
LPU00063D
1 of 4



Dr. Jarvik: Just because I'm a doctor doesn't mean I don't worry about my cholesterol.

AVO: Inventor of the Jarvik Artificial Heart, Doctor Robert Jarvik.

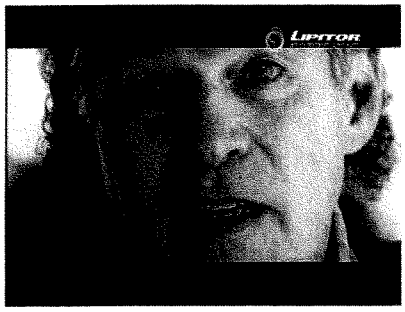
Super: Inventor of the Jarvik Artificial Heart, Doctor Robert Jarvik.



Dr. Jarvik: For many people like me, diet and exercise aren't enough.

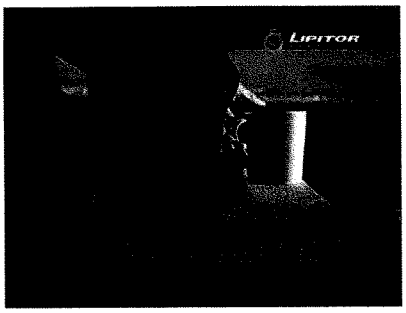
But adding Lipitor significantly lowers bad cholesterol 39-60%.

Super: Average effect depending on dose.

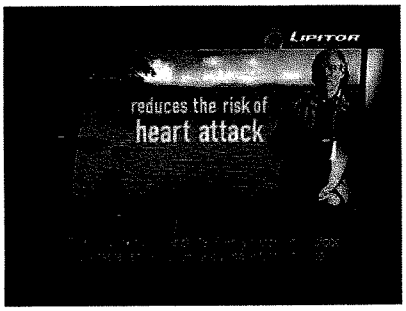


Dr. Jarvik: I take it because it does more than that.

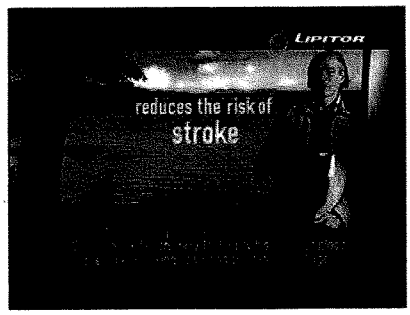
Lipitor – Pfizer
Breakfast TV :60
PFLI7016
LPU00063D
2 of 4



Unlike some cholesterol medicines, Lipitor is FDA approved..

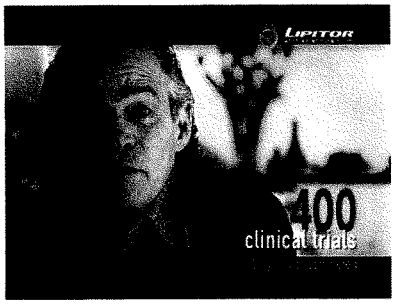


to reduce the risk of heart attack…



and stroke, if you have several common risk factors for heart disease.

Lipitor – Pfizer
Breakfast TV :60
PFLI7016
LPU00063D
3 of 4



And Lipitor is one of the most researched medicines. You don't have to be a doctor to appreciate that.



Lipitor is not for everyone, including people with liver problems and women who are nursing, pregnant or may become pregnant.

Super: See our ad in Health Magazine



You need simple blood tests to check for liver problems.

Super: 1.888.LIPITOR
Super: www.lipitor.com

Lipitor – Pfizer
Breakfast TV :60
PFLI7016
LPU00063D
4 of 4



Tell your doctor if you are taking other medications, or if you have any muscle pain or weakness. This may be a sign of a rare but serious side effect.



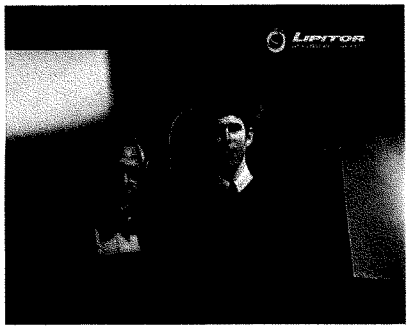
Lipitor is one of many treatment options to consider with your doctor.

Super: Available by prescription only.

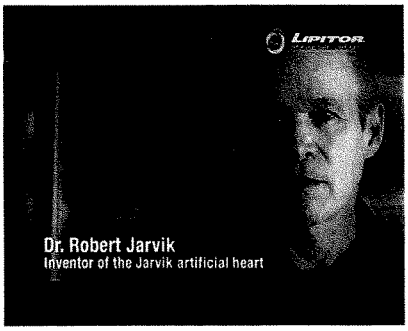


Lowering cholesterol is important. But could you be doing more...with Lipitor? Ask your doctor. Don't wait.

Pfizer - Lipitor
Father TV :60
PFLI7406
LPU00063K
1 of 5

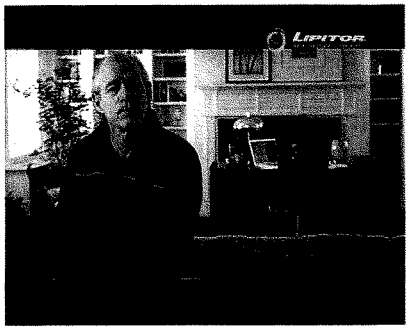


Dr. Jarvik: In college I wanted to be an architect. But after my father had a heart attack I devoted my life to studying the heart.



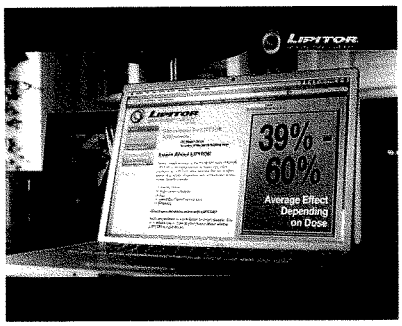
V/O : Inventor of the Jarvik Artifical Heart, Dr. Robert Jarvik.

Super: Inventor of the Jarvik artificial heart, Dr. Robert Jarvik.



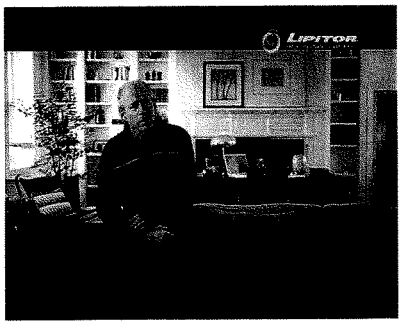
Dr. Jarvik: Now I trust my heart to Lipitor.

Pfizer - Lipitor
Father TV :60
PFLI7406
LPU00063K
2 of 5

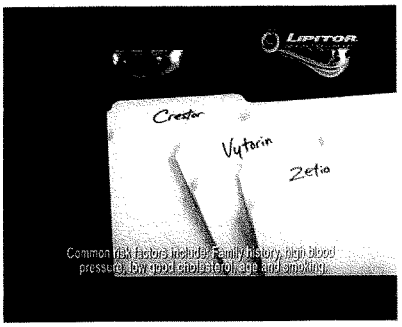


Adding Lipitor lowers bad cholesterol 39-60%, when diet and exercise aren't enough.

Super: Average effect depending on dose.



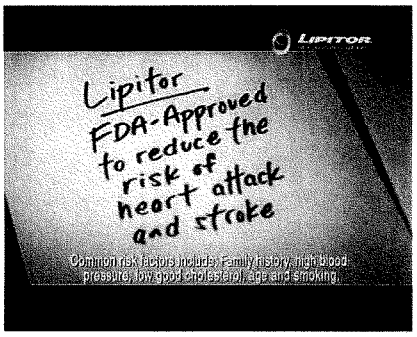
And Lipitor does more.



Unlike Crestor, Vytorin and Zetia,

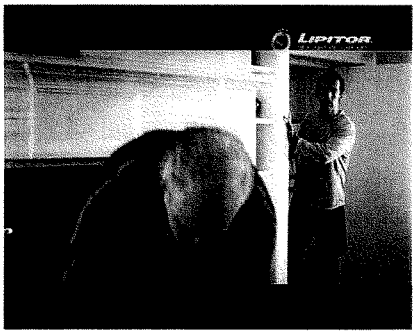
Super: Common risk factors include: family history, high blood pressure, low good cholesterol, age and smoking.

Pfizer - Lipitor
Father TV :60
PFLI7406
LPU00063K
3 of 5

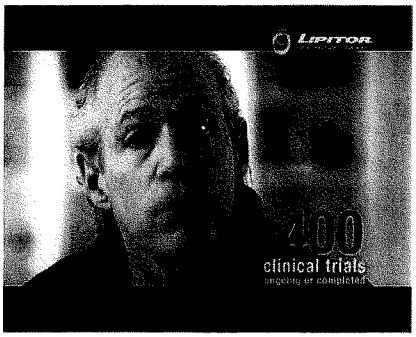


Lipitor is FDA approved
to reduce the risk of heart attack and stroke if you have several common risk factors for heart disease.

Super: Common risk factors include: family history, high blood pressure, low good cholesterol, age and smoking.



Son: Ready dad?
Dr. Jarvik: Yup

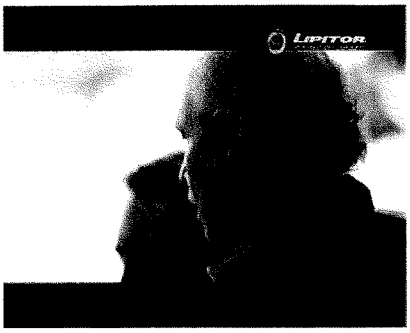


Dr. Jarvik: And Lipitor is one of the most researched medicines.

Super: 400 Clinical Trials ongoing or completed.

KTG 000023

Pfizer – Lipitor
Father TV :60
PFLI7356
LPU00063K
4 of 5



I'm glad I take Lipitor. As a doctor and a dad.



Lipitor is not for everyone, including people with liver problems and women who are nursing, pregnant or may become pregnant.

Super: See our ad in *Health* Magazine

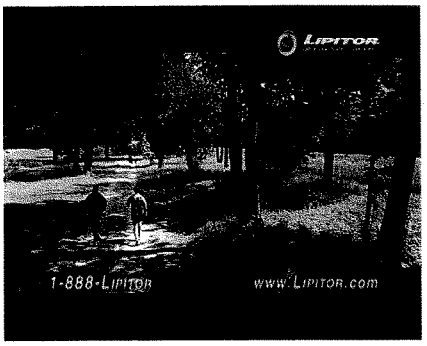


You need simple blood tests to check for liver problems.

Super: 1.888.LIPITOR
Super: www.lipitor.com

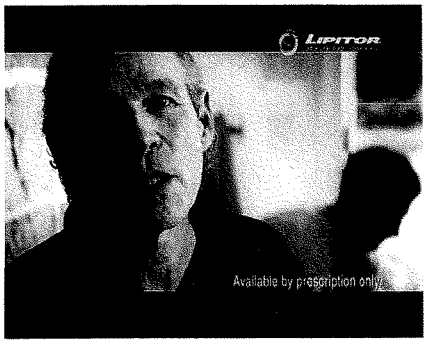
KTG 000024

Pfizer - Lipitor
Father TV :60
PFLI7406
LPU00063K
5 of 5



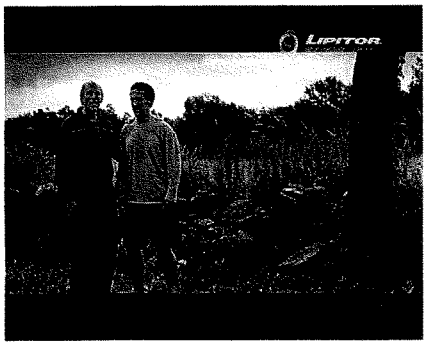
Dr. Jarvik: Tell your doctor if you are taking other medications, or if you have any muscle pain or weakness. This may be a sign of a rare but serious side effect.

Super: 1.888.LIPITOR
Super: www.lipitor.com



Lipitor is one of many treatment options to consider with your doctor.

Super: Available by prescription only.



Don't wait. Ask your doctor.

KTG 000025

PFIZER, INC.
235 East 42nd Street
Mailstop 235/10/45
New York, New York 10017

As of April 13, 2006

Robert Jarvik, M.D.
c/o Jarvik Heart Inc.
333 West 52nd Street
New York, NY 10019

Dear Dr. Jarvik:

The following will constitute the agreement (the "Agreement") between Robert Jarvik, M.D. ("Artist") and Pfizer, Inc. ("Company"), by which Artist agrees to provide his personal services as, among other things, an on-camera spokesperson for and endorsing Company's product known as Lipitor® (atorvastatin calcium) ("Product") and otherwise appear in and in connection with the production of advertising, sales, informational, promotion, marketing and publicity materials for the Product, upon the following terms and conditions:

1. **TERM**

(a) **First Term.** The initial term of the Agreement shall commence on the date hereof and shall continue thereafter in full force and effect for a period of one (1) year from the initial public broadcast use of any of the advertising materials produced hereunder ("First Term"). Solely for the purpose of calculating the date of expiration of the First Term, it is understood and agreed that the date of such initial public broadcast was March 31, 2006.

(b) **Options.** Company shall have the right at its sole option to extend the term of this Agreement, upon all of the same terms and conditions hereof, except as otherwise specifically set forth herein, for an additional consecutive one (1) year period commencing immediately upon the expiration of the preceding period, by giving written notice to Artist to such effect no later than thirty (30) days prior to the expiration of the First Term. Such additional term is hereafter called the "Second Term."

(c) The First Term and Second Term (if any) are sometimes hereafter individually referred to as a "Term" and the entire length of the Agreement is referred to as the "term".

2. **SERVICES/SPOKESPERSON MESSAGING**

(a) **Production of Advertising Materials.** Company shall have the right to utilize Artist's services and Artist shall render said services in the production of advertising, sales, informational, promotion, marketing and publicity materials and other materials for Company as follows:

(i) During each of the First Term and Second Term (if any), for up to nine (9) non-consecutive or consecutive days (in Company's sole discretion) of up to twelve(12) hours per day (each, a "Work Day", and collectively "Work Days") (exclusive of travel, rehearsals, voice-over sessions and activities relating to public relations and media training) (A) as an on-camera performer in and in connection with the production of as many television commercials, radio commercials, online commercials and other commercials as Company may elect ("Commercials"), and (B) in and in connection with still photography sessions for the purpose of producing any number and type of print materials, including, without limitation, non-broadcast consumer and trade print advertisements, publicity, collateral materials, posters, displays, point-of-sale advertising, outdoor advertising, billboards, packaging, products inserts, catalogues, brochures, online advertisements, out-of-home advertisements, industrial, patient education and physician promotional materials, media training sessions and sales force materials ("Non Broadcast Materials"), and all revisions and remakes of Commercials and Non Broadcast Materials as Company shall require in its sole discretion.

(ii) Further, during each Term, Company shall have the right to utilize Artist's services, and Artist shall render said services in the production of Commercials or for any other purpose herein, for up to four (4) voiceover sessions, each session up to two (2) hours in duration, which such sessions shall be in addition to the Work Days set forth above.

(iii) In addition, subject to Section 2(d) below and on condition that Artist is paid the additional compensation set forth in Section 4(f) below, Artist shall attend such reasonable number of rerecording sessions of up to two (2) hours in length as Company may request in connection with the production of the Commercials in which Artist originally rendered services ("Rerecording Sessions"). The Rerecording sessions shall not be considered Work Days.

(iv) In Company's sole discretion, the Commercials and Non Broadcast Materials may be produced, created and made by any process, instrumentation or device now known or hereafter developed.

(v) Company shall have the right to make or cause to be made such number of Commercials and Non Broadcast Materials as it may elect by editing, dubbing, adding to, subtracting from, compiling and integrating any or all of Artist's performances hereunder, and shall also have the right to produce

a "lift" from the audio track of a television commercial or to record during the production of a television commercial a version of the television commercial, both for radio or other use. Company shall specifically, without limitation, have the right to use film clips taken from any television commercial footage produced hereunder in the production of any Non Broadcast Materials and to use any work produced during the production of the Non Broadcast Materials in the Commercials.

(b) **Personal Appearances/Media.** During each of the First Term and Second Term, if any, Artist shall appear for up to three (3) days for miscellaneous public relations *(excluding speeches or lectures)*, and/or personal appearances on behalf of Company at functions designated by Company, and including, but not limited to, media interviews, sales meetings, conventions, and professional conferences. In addition to the three (3) days set forth in the preceding sentence, Artist shall appear for up to an additional eight (8) hours per each Term, for purposes related to media training and orientation. Such media training and orientation may occur on one (1) day or may occur over several days, provided that the total aggregate time in connection therewith shall not exceed eight (8) hours per Term.

(c) **Work Sessions and Rehearsals.** Artist shall (i) to attend all customary and reasonable rehearsals as Company may request, which shall consist of a minimum of one (1) day of rehearsal and/or consultation with the creative teams of Company and/or its agents (including, without limitation, directors, photographers, advertising agencies and the like) prior to each television and/or print shoot, on such dates and at such times and places (or via telephone, unless Company reasonably requires in person) as Company shall specify; (ii) to render services in connection with the production of the Commercials and Non Broadcast Materials in a first-class, competent and painstaking manner as directed by Company. Artist further Artist's services will be subject to Company's direction and control at all times and that Artist will promptly comply with whatever reasonable instructions, suggestions and recommendations that Company may give Artist in connection with the rendition of such services. Company shall notify Artist of the designated times and dates on which Artist's services are required as far in advance as practicable, but in all events at least forty-eight (48) hours prior to such times and dates. Artist will notify Company within twenty-four (24) hours of Artist's unavailability due only to a previously scheduled, reasonable, bona-fide professional commitment or illness that would prevent Artist from rendering Artist's services hereunder and in such event, Company shall reschedule the initial time and date for such other time and date as Company designates subject to Artist's previously scheduled, reasonable, bona fide professional commitments. Artist shall use good faith efforts to be available on such rescheduled times and dates. Artist hereby acknowledges that the shooting dates for Commercials and/or Non Broadcast Materials commenced on March 13, 2006.

(d) If, for reasons beyond Company's control any of the Commercials or Non Broadcast Materials produced hereunder are damaged or destroyed, Artist shall be available for a reasonable amount of re-shoots and/or re-recording sessions at no additional cost to Company.

(e) It is the essence of the Agreement that in connection with Artist's services to be provided hereunder Artist agrees that throughout the term, Artist will appear and perform as a spokesperson for the Product and related Product properties, shall provide an endorsement for the Product, and shall deliver specific, detailed messages and claims with respect to the efficacy and safety of the Product and Artist's preference for the Product, along with information with respect to the Product's risks and side effects, as directed by Company, subject to Artist's reasonable approval of any statement by Artist as set forth in Paragraph 8(a) below. Failure or inability by Artist to comply with or fulfill the foregoing obligation shall be considered a material breach of this Agreement.

3. OWNERSHIP, USE AND TERRITORY

(a) All materials produced in connection with the Agreement, including advertising ideas, phrases or words, visual descriptions, illustrations, photographs, music, footage and all Commercials and Non Broadcast Materials and all versions, outtakes, revisions and drafts thereof will be and remain the absolute and exclusive property of Company in perpetuity (collectively, "Advertising Materials"). Artist acknowledges that Artist's performance and the resulting proceeds of such performances are "works made for hire" under United States Copyright law and analogous laws outside the United States, and that Artist shall not have nor shall Artist claim to have any right, title or interest of any kind or nature whatsoever in such materials, or in or to any component part, element, character or characterization thereof. If, however, Artist's performance is not considered a work for hire, or if necessary in order to otherwise effectuate the purposes of this Agreement, then Artist hereby assigns all right, title and interest to all Advertising Materials, including the Commercials and Non Broadcast Materials, to Company. Artist shall not have the right to use Company's name, trademarks or intellectual or other property of any kind, including the trademarks, logos or other identifying marks of the Product, without the prior express written consent of Company.

(b) Except as otherwise provided herein, Company shall have the full and complete right, during the term hereof, to broadcast, use, reproduce, publish, copyright and/or exhibit the Commercials and the Non Broadcast Materials, and any and all versions or revisions thereof, and all other materials created or produced hereunder, whether produced in the then current Term or any earlier Term, in the following media: broadcast media (including, without limitation, national network, spot, cable, cinema, and syndication television, and national, spot, syndication and satellite radio), the internet (including, without limitation, website design, online advertising and electronic mail), wireless applications (including without limitation, i-pod casting and cell phones), video-on-demand, internal Company communications, annual reports, Industrial purposes (including without limitation, marketing conferences), print, press materials, out-of-home (on all formats), collateral (including, without limitation, all patient education materials, interactive voice recordings (IVR), physician promotion materials, Company sales force communications, sell sheets, brochures) and direct mail, throughout the United States, Canada, and Mexico and their respective territories, possessions, military bases and commonwealths (including Puerto Rico) (the foregoing shall collectively be defined as "Territory") including the right to use the same at any conventions or sales, distributor or institutional meetings sponsored or attended by Company or its dealers or distributors outside

the Territory. The Territory with respect to any and all Commercials or Non Broadcast Materials available for online viewing shall be the Universe. Company shall be entitled to utilize any materials produced or created hereunder only in conjunction and/or affiliation with the Product. Without otherwise limiting the foregoing, Company shall not utilize Artist's name or likeness in such a manner as to convey the impression that Artist is personally communicating directly with the consumer via electronic mail or other interactive means.

(c) The fact that any Non Broadcast Materials or Commercials remain on public display after the term through no fault of Company shall not give rise to any claim by Artist against Company, provided that Company shall use reasonable commercial efforts to notify any relevant distribution channels that such material must be removed. Subsequent to the expiration of the term, Company shall not be prohibited from mentioning the fact that Artist was previously a spokesperson for the Product.

4. **CONSIDERATION**

(a) In full consideration for Artist's performance of the provisions of this Agreement and for all of the rights granted by Artist hereunder, the following amount shall be payable to Artist:

(i) During the First Term: the guaranteed sum of Five Hundred and Fifty Thousand Dollars ($550,000).

(ii) During the Second Term, if any: the guaranteed sum of Eight Hundred Thousand Dollars ($800,000).

(b) The total of the guaranteed sum owing for Commercials and the sums owing for Non Broadcast Materials and personal appearances in a Term shall collectively be referred to as the "Total Payment". Subject to Artist's fulfillment of all terms and conditions of this Agreement, and unless otherwise adjusted in accordance with the terms and conditions set forth herein, the Total Payment for the First Term shall be payable as follows:

(i) Two Hundred Seventy Five Thousand Dollars ($275,000), payable within fifteen (15) business days following the later of (a) full execution hereof and (b) satisfactory completion by Artist of the first Work Day hereunder; and

(ii) Two Hundred Seventy Five Thousand Dollars ($275,000), payable within ten (10) business days following the later of (a) the date six months from the first public broadcast use of any of the Advertising Materials produced hereunder and (b) the satisfactory completion by Artist of an aggregate of five (5) Work Days hereunder, but in any event, no later than October 30, 2006.

The Total Payment for the Second Term (if any) shall be paid according to a schedule reasonably determined by Company, but in no event shall such schedule be less favorable than the schedule for the First Term.

(c) Notwithstanding that Artist is not presently a member of any union or guild having jurisdiction over the services performed hereunder (as set forth in Paragraph 8(b) below), all payments due under the applicable collective bargaining agreement shall be credited at double scale, with travel credited at scale, against the guaranteed sums set forth in paragraphs 4(a) (i) and (ii) above which are allocable to Artist's broadcast services hereunder. If at any time the sums payable pursuant to this paragraph 4(c) shall exceed the guaranteed sums, then Company shall promptly pay such excess to Artist in accordance with the terms of the applicable collective bargaining agreement.

(d) Notwithstanding that Artist is not presently a member of any union or guild having jurisdiction over the services performed hereunder (as set forth in Paragraph 8(b) below), Company shall pay directly to the Pension and Health Plan of SAG and/or the Health and Retirement Fund of AFTRA the appropriate contributions which payments shall be in addition to any other payments provided for herein.

(e) If it is necessary for Artist to travel from the area Artist is in to render Artist's services hereunder, Company shall provide Artist with round trip first class air fare for two people (inclusive of Artist) (provided that general commercial first class air transportation is available from Artist's location), along with hotel accommodations for two people, local ground transportation and properly vouchered and necessary living expenses up to a maximum of One Hundred Dollars ($100) per day in the aggregate for one person (i.e., Artist only), or, in Company's discretion, Company may reimburse Artist for such expenses, provided that such expenses are reasonable and approved by Company in advance, in writing. Artist shall not incur any expenses without Company's prior written consent.

(f) In the event Company shall, in Company's sole discretion, require additional Work Days from Artist ("Additional Work Days"), Artist shall perform services for up to five (5) such Additional Work Days (each day up to twelve (12) hours), at the rate of Eight Thousand Dollars ($8,000) per each such Additional Work Day. In the event Artist's services are required for four (4) hours or less for any such session, Artist's services in connection therewith shall be payable *pro rata* (not less than Four Thousand Dollars per day), and such session shall only be counted as one half (1/2) of one Additional Work Day. Additional Work Days shall be scheduled subject only to Artist's reasonable availability. In the event Company shall, in Company's sole discretion pursuant to Section 2A(iii), require Rerecording Days from Artist, Company shall pay Artist Two Thousand Dollars ($2,000) per each such Rerecording Day.

(g) All payments pursuant to this Agreement shall be made payable to Artist at the address set forth above unless otherwise provided for in writing and such payments shall include all payments due to Artist, Artist's agent, manager, broker and any

other third party acting on behalf of Artist, or seeking payment from Artist, and shall otherwise fully satisfy all of Company's obligations hereunder.

5. NAME AND LIKENESS

During the term hereof, Company shall have the right to use and permit the use of Artist's name, photograph, likeness, endorsement, voice and biographical material and/or frames from the Commercials and/or photographs of the production of the Commercials and Non Broadcast Materials in the Commercials and Non Broadcast Materials, and for purposes of advertising, sales, trade, promotion, marketing, informational purposes and publicity and for all other uses as set forth herein. Company shall have the right to identify to the trade, public and press that Artist is the voice in the Commercials.

6. COMPANY'S RIGHT TO TERMINATE

(a) Events of Force Majeure; Disability; Death:

(i) If for any reason beyond Company's control, such as boycotts, war, acts of God, labor troubles, strikes, restraints of public authority, terrorism or terrorist-related activity, or any similar or dissimilar occurrence (each, an "Event of Force Majeure"), Company is prevented from having Artist render Artist's services hereunder or from producing or using the Commercials or the Non Broadcast Materials, then Company shall have the right to extend the applicable Term for a period of time equivalent to the duration of such Event of Force Majeure, with no further payment owing to Artist therefore, it being agreed that no such extension of the applicable Term will exceed ninety (90) days.

(ii) In the event that Artist suffers any mental or physical disability or illness during the Term which prevents Company from utilizing Artist's services hereunder (subject to the parties' good faith efforts to reschedule any services so affected), Company shall have the right, but not the obligation, to terminate this Agreement, and the Total Payment owing to Artist for the Term during which such termination occurs shall be adjusted as described in paragraph 6(d) below.

(iii) In the event of Artist's death during the Term, Company shall have the right, but not the obligation, to terminate this Agreement, and the Total Payment owing to Artist for the Term during which such termination occurs shall be adjusted as described in paragraph 6(d) below.

(b) If Artist shall: (i) materially breach the terms of this Agreement, or (ii) fail, neglect or refuse to perform any of the obligations to be performed by Artist hereunder

(including, without limitation, failing to appear for service days or to reasonably reschedule such service days), or (iii) have committed or shall commit any act or do anything that (A) is or shall be an offense involving moral turpitude or constituting a felony, or (B) which brings Artist or Company into public disrepute, contempt, scandal, or ridicule, or (C) which insults or offends the community or any substantial organized group thereof, or (D) which might tend to embarrass Company, bring about negative reporting of Company, or injure the success of Company or any of Company's products or services, or (iv) deliver conflicting, controversial or inappropriate messaging with respect to any advertising campaign for Product, or (v) subject to Artist's reasonable approval as set forth in Paragraph 8(a) below, fail to deliver appropriate messages as directed by Company with respect to any advertising campaign for Product, or (vi) convey attitudes or opinions toward Artist's own heart health or others' heart health that is inconsistent with any advertising campaign with respect to Product, then within thirty (30) days from the time the Company learns of any such act or omission or of Artist's intent to commit such act or omission, Company shall have the right (but not the obligation), at its sole option, in addition to its other legal and other remedies, to terminate this Agreement by written notice to Artist to that effect and the Total Payment owing to Artist for the Term during which such termination takes place shall be adjusted as described in paragraph 6(d) below. Company's decision on all matters arising under this paragraph shall be conclusive but shall be exercised in good faith.

(c) If Artist's appearance or health changes materially during the term of the Agreement, including, but not limited to, an individual or discrete incident involving Artist's health, or a change in overall health, weight or hairstyle from that which exists as of the date hereof, and Company reasonably deems such change an inability to render services which is incapable of being cured within a reasonable period of time, then Company, in its good faith discretion, shall have the right (but not the obligation), in addition to its other legal and other remedies, either to extend the term of this Agreement for a period of time equivalent to Artist's inability to render services, with no further payment owing to Artist therefore (it being agreed that no such extension of the applicable Term will exceed one hundred and eighty (180) days), or to terminate the Agreement forthwith, in which case the Total Payment owing to Artist for the Term during which such termination occurs shall be adjusted as described in paragraph 6(d) below.

(d) If Company should terminate this Agreement pursuant to paragraph 6(a), 6(b), 6(c) or 6(f)(ii), the Total Payment due hereunder to Artist in respect of the then current Term shall be allocated 50% thereof to the number of Work Days completed by the date of termination (with the maximum nine (9) Work Days in the Term to be the denominator) and 50% thereof to usage (with such 50% usage allocation to be multiplied by a fraction, the numerator of which is the number of days which have been completed in the Term and the denominator of which is the total number of days in the Term). Artist shall promptly remit payments in excess of the amount due hereunder, if any, to Company.

(e) Artist hereby acknowledges that this Agreement is contingent upon Company undertaking and receiving a satisfactory criminal background check of Artist. Artist hereby agrees to provide Company with any and all requested information in order for

Company or an agent acting on Company's behalf to undertake such background check. In the event Artist does not pass such background check in Company's sole discretion, Company shall have the right, but not the obligation, to terminate this Agreement and Artist and Supplier shall return to Company any and all monies paid to Artist by Company in connection herewith. Upon any termination pursuant to this paragraph, Company shall cease using any and all materials created from the product of Artist's services hereunder.

(f) Artist hereby specifically acknowledges that this Agreement is contingent upon the United States Food and Drug Administration, on an ongoing basis throughout the Term of this Agreement, furnishing timely, full and unqualified approval with respect to the Advertising Materials, advertising campaigns and other materials featuring Artist and Product as contemplated hereunder. In the event Company does not receive such timely, full and unqualified approval, Company shall have the right to terminate this Agreement at any time, in accordance with the following: (i) in the event such termination occurs prior to the satisfactory completion by Artist of one Work Day hereunder, no payments or monies whatsoever shall be due Artist and Artist shall promptly return to Company any and all payments furnished by Company hereunder, and (ii) in the event such termination occurs subsequent to the satisfactory completion by Artist of at least one Work Day hereunder, the Total Payment owing to Artist shall be adjusted in accordance with paragraph 6(d) above.

(e) Nothing contained in this paragraph 6 shall affect or limit any other right or remedy, at law or in equity, which may otherwise be available to Company.

7. **REPRESENTATIONS AND WARRANTIES**.

Artist hereby represents and warrants that:

(a) **Competitive Protection**. Artist has not heretofore rendered any services, directly or indirectly, in or in connection with commercials or advertisements on behalf of any product competitive to or incompatible with the Product or Company's products or services the utilization of which commercials or advertisements may occur during the term. ("Competitive Products/Services"). Artist will not, at any time during the period which Company is entitled to use the Advertising Materials produced pursuant to this Agreement: (i) render any services of any kind, directly or indirectly, for any of the following: any and all pharmaceutical products whatsoever; or any other product or service of any kind making any therapeutic claim, including, without limitation, any food, drug or supplement making cardiovascular claims or claims related to cardiovascular health (the foregoing shall collectively be defined as "Excluded Products/Services"), or (ii) authorize the use of Artist's name, photograph, likeness, endorsement, voice or biographical material in any manner in or in connection with the sale, advertising, publicity, marketing or promotion of any kind in connection with an Excluded Product/Service. Without otherwise limiting any of Company's rights herein, Excluded Products/Services shall not include the medical or scientific purposes associated with inventions, writings, scientific research and medical-related devices attributed solely to Artist.

(b) **Compliance With Law.** Artist will comply with all applicable laws, regulations, orders and ordinances in rendering the services provided for herein and all such services rendered by Artist shall be promptly rendered and shall be of first quality.

(c) **Right to Enter Agreement.** Artist has full power and authority to enter into this Agreement and to perform all of the obligations hereunder without violating the legal or equitable rights of any third party.

(d) **Confidential Information.** Artist shall not disclose to any party or utilize any confidential or proprietary information obtained hereunder regarding Company or its products or services, including, without limitation, the subject matter, terms or existence of this Agreement. Artist shall not make any announcement, public or otherwise, with respect to this Agreement, Artist's services to be rendered hereunder, or any matter whatsoever with respect to Company, without the express prior written consent of Company, without limitation to Artist's right to review all press releases pursuant to Paragraph 8(a) below.

(e) **Comparative Advertising.** Artist recognizes that Artist is rendering valuable services to Company, in the creation of goodwill for Company and its products. Accordingly, Artist agrees that, during the Term of the Agreement, Artist will not render Artist's services or permit the use of Artist's name, recorded voice, likeness, photograph or biography in advertising or publicity for anyone else in the Territory where such advertising or publicity damages said goodwill by demeaning or denigrating, directly or indirectly, Company or any of its products.

(f) **Testimonial Affidavits.** If, and to the extent that Company shall require testimonial affidavits or other documentation for the purpose of complying with legal or broadcaster or publisher requirements concerning the use of testimonials and endorsements in advertising, Artist shall furnish appropriate affidavits or appropriate documentation attesting to Artist's preference for the Product or as may otherwise be required.

(f) **Insurance.** Company shall have the right to protect its interest hereunder by taking out an insurance policy, at Company's cost, on the life of Artist. Artist agrees that if necessary, Artist shall attend any reasonable physical examinations that may be necessary to obtain said policy. If Artist so desires and if permitted by the insurance carrier, Artist shall have the right to have a doctor of Artist's choice present at any such examination at Artist's own expense.

8. **GENERAL PROVISIONS**

(a) **Publication of Advertising Material** Company shall be under no obligation to cause the Commercials or Non Broadcast Materials produced hereunder to be used or broadcast, it being understood that the sole obligation of Company is to make such payments as are required under this Agreement. Other than as specifically set forth herein, Artist waives any right to inspect or approve the Commercials and Non Broadcast Materials

and Company shall have no liability for any visualization which may occur to the Commercials or Non Broadcast Materials, including, but not limited to blurring, distortion, alteration or optical illusion. Company agrees that Company shall consult with Artist with respect to Artist's services to be provided hereunder provided that in all events, Company shall have final approval in its sole discretion with respect to all Commercials, Non Broadcast Materials and other materials produced, created or distributed hereunder, all elements incorporated therein and related thereto (including, without limitation, scripts); and all uses to which the foregoing may be applied. Company shall not be required to obtain Artist's approval in connection with any of the foregoing. Notwithstanding the foregoing, Artist shall have the right, in Artist's discretion, to refuse to have a statement attributed to Artist if Artist believes in good faith that such statement is untrue. In the event Company, in its sole discretion, requests approval from Artist with respect to any materials or any particular element, Artist shall provide comments, if any, in writing, within twenty four (24) hours of Artist's receipt of such materials or element. In connection with the preceding sentence, Artist shall have the right to review all press releases prior to the general commercial distribution of such releases.

(b) **Union Membership.** Company acknowledges that Artist is not presently a member of the Screen Actors Guild, AFTRA or any other union or guild having jurisdiction over Company and the services performed by Artist hereunder, and Company shall be responsible for any penalties imposed by any such unions or guilds with respect to the services performed by Artist hereunder. This Agreement is subject to all of the terms and conditions of the collective bargaining agreements with SAG and AFTRA and any other union agreements or codes having jurisdiction over Artist's services hereunder. To the extent that any applicable collective bargaining agreement shall require any additional compensation to Artist with respect to Artist's services, whether for travel, rehearsal time, wardrobe fittings, make-up or any or all other types of compensation now or in the future contained in said agreements, such compensation shall be deemed paid by the guaranteed sums provided in paragraphs 4(a)(i) and (ii) above with respect to the respective Term.

(c) **Indemnity.**

(i) Company shall defend, indemnify and hold harmless Artist from and against any and all third party claims, damages, costs, judgments, penalties and expenses (including, without limitations, reasonable legal fees and disbursements) arising out of or in connection with (i) the production, broadcast, cablecast or other use by Company of the materials produced by Company pursuant to this Agreement (including, without limitation, as a result of any representations made by Company in any Commercials or Non Broadcast Materials produced by Company hereunder) and/or (ii) Company's products and services (including, without limitation, any product liability actions related to Company's products or services brought against Artist or Company), except to the extent any damages, costs, judgments, penalties and expenses are due to any tortious conduct or intentional misconduct of Artist.

(ii) Artist shall defend, indemnify and hold harmless Company from and against any and all damages, costs, judgments, penalties and expenses of any kind

(including reasonable legal fees and disbursements) which may be obtained against, imposed upon or suffered by Company as a result of the breach by Artist of this Agreement or any of the warranties and representations made herein or as a result of any representation, information or material supplied by either Artist to Company in connection herewith.

(d) Nature of Services. It is expressly understood and agreed that the services to be performed by Artist and the rights and privileges granted to Company hereunder are special, unique, extraordinary and impossible of replacement, which gives them a peculiar value, the loss of which could not be reasonably or adequately compensated in damages in an action of law, and that Artist's failure or refusal to perform Artist's obligations hereunder would cause Company to suffer irreparable loss and damage. Accordingly, Artist agrees that should Artist fail or refuse to perform such obligations, Company shall be entitled to seek *ex-parte* injunctive or other equitable relief against Artist to prevent the continuance of such failure or refusal or to prevent Artist from performing services for, or granting rights to others, in violation of this Agreement. Neither the right to resort to injunctive or other equitable relief, nor the exercise of such right, shall constitute a waiver of any other or additional rights at law or pursuant to the terms of this Agreement which Company may have against Artist as a result of such failure or refusal.

(e) No Waiver. Any failure by Company or Supplier to exercise any right granted herein upon the occurrence of any contingency set forth in this Agreement will not in any event constitute a waiver of any such right upon the occurrence of any such contingency.

(f) Interviews. Supplier agrees that neither it nor Artist will authorize or release advertising or publicity materials, nor will Artist give interviews which make reference to the details of Artist's engagement hereunder, without Company's prior written approval, although Artist may, during interviews, respond, discuss and comment in a favorable and positive manner that Artist is associated with Company and endorses its products and services.

(g) Notices. Any notice to be given by Company to Artist hereunder will be deemed sufficiently given if in writing and delivered personally or sent by certified mail or facsimile transmission to Artist or Artist's agent at the address set forth above with a copy to Richard Hofstetter, Frankfurt Kurnit Klein & Selz P.C., 488 Madison Ave., New York, NY 10022; and if the notice is to be given to Company, then by Artist forwarding same in the manner herein set forth to the attention of Donna Fernandes and, if such notice is pursuant to paragraph 2(c) hereof, Artist shall telephone Donna Fernandes at Pfizer and follow up said call by a confirming facsimile transmission. Any notice so delivered, mailed or transmitted will be deemed to be given on the date it is delivered personally, mailed or transmitted.

(h) Captions. The captions in this Agreement are inserted solely for purposes of facilitating easy reference and shall not be construed in any way as a part of the text, or as altering the substantive provisions of this Agreement.

(i) **Applicable Law.** This Agreement is made in the State of New York and shall be construed and interpreted in accordance with the internal laws of the State of New York, applicable to contracts made and performed entirely therein. Artist agrees and consents that jurisdiction and venue of all matters relating to this Agreement shall be vested exclusively in the Federal, state and local courts within the Southern District of the State of New York.

(j) **Severability.** If any provision of this Agreement is determined to be invalid by a court of competent jurisdiction, such determination shall in no way affect the validity or enforceability of any other provision herein.

(k) **Time Of the Essence.** Time is of the essence with regard to Artist's performance of the services described herein, as is Artist's appearance at all scheduled production dates and other dates scheduled with Company, subject to Artist's prior bona fide professional commitments and obligations as provided herein.

(l) **Binding Nature.** This Agreement shall be binding upon Artist and their respective successors, heirs, guardians, representatives and executors. For purposes of this Agreement, Company shall include its parent, agents, assigns, affiliates, subsidiaries and distributors ("Company Representatives"), and all rights granted to Company shall also be deemed to be granted to Company Representatives.

9. **COMPLETE AGREEMENT**

This document is a complete and exclusive statement of the terms of this Agreement and may not be changed orally but only by a writing signed by both parties hereto. Artist's signature at the end hereof, together with Company's, will constitute this a binding agreement between Artist and Company.

Very truly yours,

Pfizer, Inc.

By: _____

ACCEPTED AND AGREED:

Robert Jarvik, M.D.

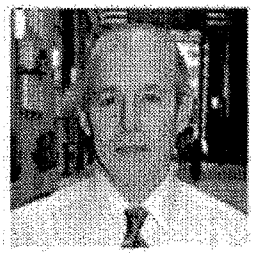
_____

Title: _____

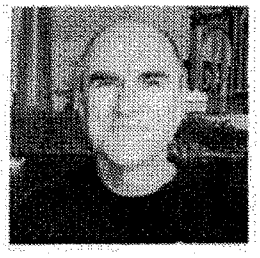
Date: 6/15/06

TALENT LIPITOR

STICKS + STONES Job# 27021



Role: Himself
Name: Dr. Robert Jarvik



Role: Skulling Double
Name: Dennis Williams
Phone: 206.784.2355
Cell: 206.669.5833
Fax:
Agent: N/A

talent PARTNERS

TALENT PARTNERS
123 WEST 18TH STREET NEW YORK, NY 10011

Invoice For: KAPLAN THALER GROUP LTD
825 8TH AVE 34TH FL
NEW YORK NY 10019-7498
ATTN: JANET WOLLMAN

Employer of Record: TALENT PARTNERS
Internal Coding: PF
SBOL AWEI AC H

Client: PFIZER
Product: LIPITOR
Commercial: ROWING
ISCII Number: ROWING

First Fixed Cycle: MAR13/06
Expiration Date: DEC12/07

Invoice # 4296 C63334

Date MAR27/06 Page 1 of
Media TV Copy 4
Estimate 086-PFLIPT65455
Comml Len 60

Pay Type SESSION
Use Type SESSION
Cycle Wks 13
Cycle MAR13/06-JUN12/06

Film Date: MAR13/06 Film Studio: STICKS&STONE Film City: SEATTLE,WA

Pid #	Performer Name	Ov%	Cat	On/ Off Cam	Agnt	St	Lft	Dbl	First Serv. Date	OT & Travl Hr.Mn	No Dy	No Sp	Yr	Apl	Inc		Amount Applied	Gross Wages	Misc. Payment	P & H
Z4FUK7	WILLIAMS DENNIS	100	EXB	ON		WA			031306	16.30	3	1	03		4	X		3903.12	96.41	558.15
Pension & Health Remittance									Apply Legend		Include Legend						Totals	3903.12	96.41	558.15

Company TALENT PARTNERS Union SAG

Account	Gross Payment	Contribution
865864-SEA	3903.12	558.15

1 Session
2 Holding Fee
3 WS Upgrade
4 Guarantee
5 Other
6 Cable

1 Wardrobe Fee
2 Meal Penalty
3 Cartage
4 Other
5 Supplies

Wages & Misc Payments	3999.53
Payroll Taxes	628.79
P & H Contribution	558.15
Sub Total	5186.47
Handling	285.26

**** Payment due in 10 days ****
Remit to: Talent Partners, 3603 Paysphere Circle, Chicago, IL 60674

Invoice Total	5471.73

KTG 000055

the kaplan thaler group, ltd.
advertising & entertainment

Producer's notes: Com'l # "Jarvik" :60 Producer MARY MORGAN

Player's Attorn.

Date(s) Worked	Time: Arrived	Time: Dismissed	Overtime	Meals: From	Meals: To	Travel Time: To	Travel Time: From	Comments
03/12/06	2P	6P				1130A		FITTINGS
03/13/06	630A	715P	5.75	1220P	1250P	6A	745P	+MILEAGE
03/14/06	630A	620P	5.25	1240P	120P	6A	715P	+MILEAGE
03/15/06	7A	~~330P~~ 1P		1230P	100P	630A	~~330P~~ 2P	330P +MILEAGE

Did performer work within past two weeks for the same product? Yes ☐ No ☑
If yes, Date _____ Com'l #1 _____
(the above notes are not terms of the following contract)

STANDARD EMPLOYMENT CONTRACT FOR TELEVISION & RADIO COMMERCIALS ☒ SAG ☐ AFTRA
Date 03/12/06

Between The Kaplan Thaler Group, Ltd. , 825 Eighth Avenue, N.Y., N.Y. 10019-7498, Producer acting as agent for
Pfizer (CLIENT) and DENNIS WILLIAMS (PERFORMER)

Producer engages Performer and Performer agrees to perform services for Producer in 1 (NUMBER) commercial(s) as follows:

A. Product(s) to be advertised Lipitor
B. Date & hour of engagement 03/13/06
at _____
C. Part to be played Extra

Check if Applicable:
☐ Cable Commercial(s)
☐ Seasonal Commercial(s)
☐ Test Market Commercial(s)
☐ "Non Air" Commercial(s)

☐ Performer does not consent to the use of his services in commercials made hereunder as dealer commercials payable at dealer commercial rates. ☐ Performer does not consent to the use of his services in commercials made hereunder on a simulcast. ☐ Performer does not consent to the use of his services in commercials made hereunder on the internet.

D. Classification: ☒ On-Camera ☐ Off-Camera ☐ Radio
☐ Actor ☐ Singer—Solo or Duo ☐ Singer—9 or more ☐ Stunt Performer ☒ Extra (other category)
☐ Announcer (com'l.) ☐ Singer—3—5 ☐ Contractor ☐ Puppeteer
☐ Announcer (billboards) ☐ Singer—6—8 ☐ Specialty Act ☐ Pilot

E. Compensation: SESSION FEE On-Camera $ double scale SESSION FEE Off-Camera _____
Special Provisions: buyout

F. Check: Wardrobe furnished by Producer ☒ Performer ☐
If Performer, # of costume changes _____ non-evening wear @ $_____ ☐
_____ evening wear @ _____ ☐

Employer of Record for Income Tax & Unemployment Insurance Purposes is: Talent Partners (for The Kaplan Thaler Group, Ltd.)

Hairdress furnished by Producer ☐ Performer ☐ Flight Insurance ($_____) check if payable ☐ Total $ _____
Fitting ☒ _____ hrs. Wardrobe Tests ☐ _____ hrs. Makeup Tests ☐ _____ Total $ _____

G. Performer instructs and authorizes producer to make checks payable to:
☒ Self at 7032 - 13th AVE NW SEATTLE WA 98117 (ADDRESS)
or
☐ Self c/o _____ (NAME) at _____ (ADDRESS)

Performer understands that payment will be made as above unless written instructions requesting a change are sent to: Talent Payment Dept., The Kaplan Thaler Group, Ltd., 825 Eighth Avenue, NY, NY 10019-7498.

H. This contract is subject to all of the terms and conditions of the applicable SAG /AFTRA Commercials Contract. The standard provisions printed on the reverse side hereof are a part of this contract. If this contract provides for compensation at minimum scale, no additions, changes or alterations may be made in the form other than those which are more favorable to the Performer than herein provided.

I. If this contract provides for compensation above minimum scale, additions may be agreed to between Producer and Performer which do not conflict with the provisions of the Commercials Contract; provided that such additional provisions are separately set forth under the "Special Provisions" rider attached hereto and made a part hereof and signed by the Performer.

J. Special Provisions: Check if rider is attached. ☐ Stunt Adjustment ☐ **Important Provisions on Back — Please read carefully**

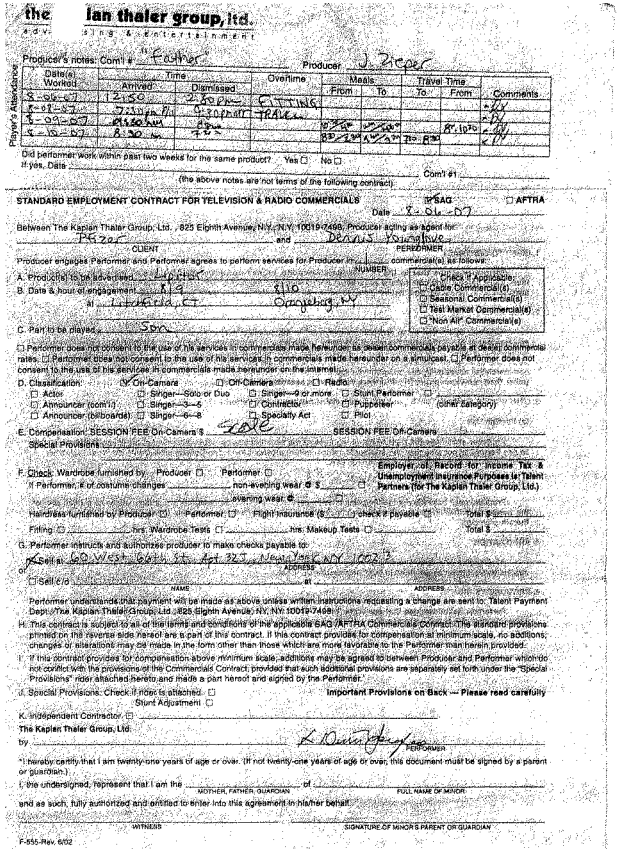
K. Independent Contractor ☐ _____

The Kaplan Thaler Group, Ltd.
by _____ ☒ _____ (PERFORMER)

"I hereby certify that I am twenty-one years of age or over. (If not twenty-one years of age or over, this document must be signed by a parent or guardian.)

I, the undersigned, represent that I am the _____ (MOTHER, FATHER, GUARDIAN) of _____ (FULL NAME OF MINOR)

KTG 000056



the adv. ian thaler group, ltd. sing & entertainment

Producer's notes: Com'l # "Father" Producer J. Riepe

Player's Attendance

Date(s) Worked	Time Arrived	Time Dismissed	Overtime	Meals From	Meals To	Travel Time To	Travel Time From	Comments
8-16-07	12:30 pm	9:30 pm	FITTING					* PU
8-17-07	7:30 am	6:30 pm	TRAVEL					* PU
8-20-07	9:30 AM	TBA		12:30	1:30		8:00	* PU
8-21-07	8:30 AM	TBA		12:30	1:30	TBA	6:30	* PU

Did performer work within past two weeks for the same product? Yes ☐ No ☐
If yes, Date _____ Com'l #1 _____
(the above notes are not terms of the following contract)

STANDARD EMPLOYMENT CONTRACT FOR TELEVISION & RADIO COMMERCIALS ☐ SAG ☐ AFTRA

Date 8-16-07

Between The Kaplan Thaler Group, Ltd., 825 Eighth Avenue, N.Y., N.Y. 10019-7499, Producer acting as agent for PEPSI CLIENT and DENNIS Yaucinto PERFORMER

Producer engages Performer and Performer agrees to perform services for Producer in ____ commercial(s) as follows:

A. Product(s) to be advertised: DIET PEPSI NUMBER

B. Date & hour of engagement 8.19 8:30 Orangeburg, NY
at Litchfield, CT

C. Part to be played: SON

Check if Applicable:
☐ Cable Commercial(s)
☐ Seasonal Commercial(s)
☐ Test Market Commercial(s)
☐ "Non Air" Commercial(s)

☐ Performer does not consent to the use of his services in commercials made hereunder as "wild" commercials payable at desig. commercial rates. ☐ Performer does not consent to the use of his services in commercials made hereunder on a simulcast. ☐ Performer does not consent to the use of his services in commercials made hereunder on the internet.

D. Classification: (X) On-Camera ☐ Off-Camera ☐ Radio

☐ Actor ☐ Singer—Solo or Duo ☐ Singer—3 or more ☐ Stunt Performer ☐ _____
☐ Announcer (cont'l) ☐ Singer—3–5 ☐ Comedian ☐ Puppeteer (other category)
☐ Announcer (billboards) ☐ Singer—6–8 ☐ Specialty Act ☐ Pilot

E. Compensation: SESSION FEE On-Camera $ SAVE SESSION FEE Off-Camera _____
Special Provisions _____

F. Check: Wardrobe furnished by: Producer ☐ Performer ☐
If Performer, \$ of costume charges _____ non-evening wear @ $ _____ ☐
evening wear @ _____ ☐

Hairdress furnished by Producer ☐ Performer ☐ Flight Insurance ($ _____) check # payable ☐ Total $ _____

Fitting ☐ _____ hrs. Wardrobe Tests ☐ _____ hrs. Makeup Tests ☐ Total $ _____

G. Performer instructs and authorizes producer to make checks payable to:
☒ Self c/o 60 West 64th St. Apt 32J New York NY 10023
ADDRESS
☐ Self c/o _____ at _____
NAME ADDRESS

Performer understands that payment will be made as above unless written instructions requesting a change are sent to: Talent Payment Dept., The Kaplan Thaler Group, Ltd., 825 Eighth Avenue, N.Y., N.Y. 10019-7499.

H. This contract is subject to all of the terms and conditions of the applicable SAG / AFTRA Commercials Contract. The standard provisions printed on the reverse side hereof are a part of this contract. If this contract provides for compensation at minimum scale, no additions, changes or alterations may be made in the form other than those which are more favorable to the Performer than herein provided.

I. If this contract provides for compensation above minimum scale, additions may be agreed to between Producer and Performer which do not conflict with the provisions of the Commercials Contract, provided that such additional provisions are separately set forth under the "Special Provisions" rider attached hereto and made a part hereof and signed by the Performer.

J. Special Provisions: Check if rider is attached. ☐ **Important Provisions on Back — Please read carefully**
Stunt Adjustment ☐

K. Independent Contractor ☐ _____

The Kaplan Thaler Group, Ltd.
by _____ L Dennis Yaucinto
PERFORMER

*I hereby certify that I am twenty-one years of age or over. (If not twenty-one years of age or over, this document must be signed by a parent or guardian.)

I, the undersigned, represent that I am the _____ of _____
MOTHER, FATHER, GUARDIAN FULL NAME OF MINOR

and as such, fully authorized and entitled to enter into this agreement in his/her behalf.

_____ _____
WITNESS SIGNATURE OF MINOR'S PARENT OR GUARDIAN

F-555-Rev. 6/02

KTG 000058

talent PARTNERS

TALENT PARTNERS
115 WEST 18TH STREET NEW YORK, NY 10011
TP FED ID 20-0467282
Employer of Record TALENT PARTNERS

Invoice For KAPLAN THALER GROUP LTD
825 8TH AVE 34TH FL
NEW YORK NY 10019-7498
ATTN: JANET WOLLMAN

Internal Coding PF LIP
SBOL AWEI AC H

Client PFIZER
Product LIPITOR CHANGE
Commercial FATHER
ISCII Number PFLI7406

First Air Date SEP10/07
First Fixed Cycle AUG09/07
Expiration Date MAY08/09

Film Date AUG09/07 Film Studio STICKSSTONES Film City LITCHFLD, CT
Record Date OCT03/07 Record Studio LOCATION Record City NYC
Music Date SEP07/07 Music Studio MACROSOUND Music City NYC
AFM Contract MR6002

Invoice # 4296 K71194

Date NOV08/07 Page 1 of 1
Media TV Copy 3
Estimate 086-PFLIPT77633
Comml Len 60

Pay Type REUSE
Use Type CLASS A NETWORK
Cycle Wks 13
Cycle SEP04/07-DEC03/07
Totl Uses 101 - 120

Class A	Date	Program Name	Lft	Net	Date	Program Name	Lft	Net	Date	Program Name	Lft	Net	Date	Program Name	Lft	Net
	OCT15	AMERICA THIS MO		A	OCT15	JUDGE JUDY (AT)		S	OCT15	DAY ROTATION		I	OCT15	MILLIONAIRE (AT		S
	OCT15	JUDGE JUDY (AT)		S	OCT15	JEOPARDY		S	OCT16	EARLY SHOW-1		C	OCT16	ABC WRLD NEWS T		A
	OCT16	ALCS GAME 4		F	OCT17	GOOD MORNING, A		A	OCT17	TODAY SHOW		N	OCT17	NBC NIGHTLY NEW		N
	OCT17	LIFE		N	OCT17	CBS EVENING NEW		C	OCT18	CBS MORNING NEW		C	OCT18	NBC NIGHTLY NEW		N
	OCT18	ALCS GAME 5		F	OCT19	EARLY SHOW-2		C	OCT19	GHOST WHISPERER		C	OCT20	SATURDAY EARLY		C

Pid #	Performer Name	Ov%	Cat	On/ Off Cam	Agnt	St	L f t	D b l	First Serv. Date	Use Range		Yr	A p l	I n c		Amount Applied	Gross Wages	Misc. Payment	P & H
CFKNMY	JARVIK ROBERT	100	P	ON		NY			080907	101-120		06	4			1978.00			
ZN54U4	YOUNGLOVE DENNIS		P	ON		CT			080907	101-120		06					989.00		146.37
N07I6Q	FREED SAM		P	OFF	2753	NY			100306	101-120		06						735.00	108.78
7KBYJ3	GEORGE BAILEY IN	CRP																	

Pension & Health Remittance

Company TALENT PARTNERS Union SAG

Account	Gross Payment	Contribution
865864-NY	1724.00	255.15

Apply Legend
1 Session
2 Holding Fee
3 WS Upgrade
4 Guarantee
5 Other
6 Cable

Include Legend
1 Wardrobe Fee
2 Meal Penalty
3 Cartage
4 Other
5 Supplies

Totals	989.00	735.00	255.15

Wages & Misc Payments	1724.00
Payroll Taxes	167.86
P & H Contribution	255.15
Sub Total	2147.01
Handling	118.09

** Payment due in 10 days **
Remit to: Talent Partners, 3603 Paysphere Circle, Chicago, IL. 60674

Invoice Total	2265.10

KTG 000076

256

RUN D :807/08 AT 10.12 Check List REQUE (JD*,4908
REPORT FACH PAGE 1
PID ZN54U4 Employer TP
YOUNGLOVE DENNIS TALENT PARTNERS

Inv/Agy	Payroll/Comm	Chk/Cli	Un-Agnt/Srv	S/R	Ap	In	Gross/Misc	Ded/Net
B80850			SAG	R			840.65	
4296	PFLI7406	PF	AUG09/07				.00	
A82229			SAG	R			567.10	
4296	PFLI7406	PF	AUG09/07				.00	
A83626	FEB06/08	22238243	SAG	R			989.00	283.64
4296	PFLI7406	PF	AUG09/07				.00	705.36
A82598	JAN30/08	22221064	SAG	R			346.15	64.70
4296	PFLI7406	PF	AUG09/07				.00	281.45
A82597	JAN23/08	22200257	SAG	R			989.00	283.64
4296	PFLI7406	PF	AUG09/07				.00	705.36
A81009	JAN17/08	22187243	SAG	R			247.25	41.00
4296	PFLI7406	PF	AUG09/07				.00	206.25
L73230	JAN07/08	22160537	SAG	R			939.55	265.28
4296	PFLI7406	PF	AUG09/07				.00	674.27
L72845	DEC27/07	22146871	SAG	R	2		1561.95	297.77
4296	PFLI7406	PF	AUG09/07				.00	1264.18
L72844	DEC27/07	22146870	SAG	R			445.05	91.19
4296	PFLI7406	PF	AUG09/07				.00	353.86
L72676	DEC20/07	22135852	SAG	R			2738.00	646.31
4296	PFLI7406	PF	AUG09/07				.00	2091.69
L71222	DEC18/07	22125570	SAG	R			247.25	41.20
4296	PFLI7406	PF	AUG09/07				.00	206.05
L71221	DEC18/07	22125569	SAG	R			939.55	266.29
4296	PFLI7406	PF	AUG09/07				.00	673.26
L70452	DEC11/07	22106071	SAG	R			791.20	211.18
4296	PFLI7406	PF	AUG09/07				.00	580.02
L70716	DEC10/07	22101505	SAG	R			1701.30	333.56
4296	PFLI7406	PF	AUG09/07				.00	1367.74
K73849	DEC06/07	22092486	SAG	R			939.55	266.29
4296	PFLI7406	PF	AUG09/07				.00	673.26
K72786	NOV29/07	22073291	SAG	R			148.35	21.09
4296	PFLI7406	PF	AUG09/07				.00	127.26

PID ZN54U4 Employer TP
YOUNGLOVE DENNIS TALENT PARTNERS

Inv/Agy	Payroll/Comm	Chk/Cli	Un-Agnt/Srv	S/R	Ap	In	Gross/Misc	Ded/Net
K72785	NOV29/07	22073290	SAG	R			989.00	285.12
4296	PFLI7406	PF	AUG09/07				.00	703.88
K71970	NOV20/07	22053801	SAG	R			642.85	152.14
4296	PFLI7406	PF	AUG09/07				.00	490.71
K71969	NOV20/07	22053800	SAG	R			247.25	41.19
4296	PFLI7406	PF	AUG09/07				.00	206.06
K71968	NOV20/07	22053799	SAG	R			989.00	285.12
4296	PFLI7406	PF	AUG09/07				.00	703.88
K71197	NOV13/07	22034575	SAG	R			98.90	12.36
4296	PFLI7406	PF	AUG09/07				.00	86.54
K71196	NOV13/07	22034574	SAG	R			989.00	285.12
4296	PFLI7406	PF	AUG09/07				.00	703.88
K71195	NOV09/07	22026892	SAG	R			989.00	285.12
4296	PFLI7406	PF	AUG09/07				.00	703.88
K71194	NOV09/07	22026891	SAG	R			989.00	285.11
4296	PFLI7406	PF	AUG09/07				.00	703.89
I73857	NOV08/07	22023811	SAG	R			567.10	128.12
4296	PFLI7406	PF	AUG09/07				.00	438.98
J74299	OCT31/07	22001072	SAG	R			296.70	52.76
4296	PFLI7406	PF	AUG09/07				.00	243.94
J74298	OCT31/07	22001071	SAG	R			989.00	285.12
4296	PFLI7406	PF	AUG09/07				.00	703.88
J71899	OCT23/07	21976169	SAG	R			346.15	65.09
4296	PFLI7406	PF	AUG09/07				.00	281.06
J71898	OCT23/07	21976168	SAG	R			989.00	285.12
4296	PFLI7406	PF	AUG09/07				.00	703.88
I72970	SEP26/07	21900961	SAG	R			2738.00	646.31
4296	PFLI7406	PF	AUG09/07				.00	2091.69
I72924	SEP26/07	21900960	SAG	R			494.50	105.32
4296	PFLI7406	PF	AUG09/07				.00	389.18
I72923	SEP26/07	21900959	SAG	R			989.00	285.12
4296	PFLI7406	PF	AUG09/07				.00	703.88

RUN O 807/08 AT 10.12 Check List REQUE JD*,4908
REPORT ACH PAGE 3
PID ZN54U4 Employer TP
YOUNGLOVE DENNIS TALENT PARTNERS

Inv/Agy	Payroll/Comm	Chk/Cli	Un-Agnt/Srv	S/R	Ap	In	Gross/Misc	Ded/Net
I72693	SEP26/07	21900958	SAG	R	1		1463.05	272.54
4296	PFLI7406	PF	AUG09/07				.00	1190.51
H71907	AUG27/07	21821649	SAG	S			2463.40	560.50
4296	FATHER	PF	AUG09/07				.00	1902.90
			Totals			31700.80	7430.42	
							.00	22862.63

34 CHECK RECORDS

Utah Artificial Heart Institute

Don B. Olsen, D.V.M.
President
801-323-1122
dolsen@uahi.org

August 10, 2006

Mr. Jeffrey B. Kindler
Chairman and Chief Executive Officer
Pfizer Inc.
235 East 42nd Street
New York, New York 10017

As longtime investigators in mechanical methods of treating the failing heart, we write to ask you to correct an inaccuracy in the current extensive advertising for Lipitor. We respect Dr. Jarvik's contributions in circulatory assist devices, but Dr. Jarvik was *not the inventor of the artificial heart.* For the artificial heart implanted in Utah, that distinction belongs to Willem J. Kolff, MD, PhD and Tetsuzo Akutsu, MD, PhD.

Dr. Kolff's work on an artificial heart was begun at the Cleveland Clinic in ~1957 and, in 1967, continued at the University of Utah. *The artificial heart design went through numerous iterations.* As a motivating incentive to his young research collaborators, Dr. Kolff offered to name each iteration for successive design team leaders, each of whom may have added only minor changes. These team leaders included Dr. Akutsu, Dr. Yukihiko Nosé, Dr. Clifford Kwan-Gett, and Dr. Jarvik. Dr. Kwan-Gett's artificial heart was later modified by Dr. Jarvik and other members of the Utah team, including Dr. Don Olsen. Hence, the Jarvik Heart.

At the 1983 annual meeting of the American Society of Artificial Organs (ASAIO), Dr. Kolff reported that over 260 team members made contributions to the design and development of the total artificial heart before the implant was received by Dr. Barney Clark. Dr. Kolff is now 95. We would be glad to provide a bibliography documenting this history and to respond to any questions. These can be addressed to Dr. Donald B. Olsen, head of the Utah Total Artificial Heart program (dolsen@uahi.org) or to John Watson, PhD, Professor of Bioengineering at the University of California at San Diego and former NIH Artificial Heart Program Director (jtwatson@ucsd.edu).

We respectfully request that the current Lipitor ads in all media be corrected to accurately describe Dr. Jarvik's contribution as *"one of the designers (or 'a designer')* of the artificial heart", not "the inventor of the artificial heart". We trust Pfizer's high ethical standards will permit no less.

Don Olsen, DVM, Dr Sci
Pres, ASAIO 1991-1992

Yukihiko Nosé, MD, PhD
Pres, ASAIO 1992-1993

Adrian Kantrowitz, MD
Pres, ASAIO 1968-1969

803 North 300 West, Salt Lake City, Utah 84103
Tel: 801-323-1100 Fax: 801-323-1110

Pfizer Inc
235 East 42nd Street
New York, NY 10017

Pfizer Global Pharmaceuticals

Marina Pearlman
Corporate Counsel
Pfizer Inc
235 East 42nd Street
New York, NY 10017

August 28, 2006

Dr. Don B. Olsen
803 North 300 West
Salt Lake City, UT 84103

Dr. Olsen:

We recently received your letter regarding the accuracy of our current Lipitor campaign featuring Dr. Robert Jarvik as "inventor of the artificial heart". Thank you for bringing your concerns to our attention. It is never our intention to misrepresent facts or information in our communications. Nor is it our desire to diminish or refute the role of the many contributors who have influenced artificial heart design over the years. These date back to Paul Winchell's patent in 1963.

It is our belief, however, that Lipitor's depiction of Dr. Jarvik as inventor of the artificial heart is consistent with his representation throughout the scientific community as inventor of the first successful artificial heart for humans. In 1982 the "Jarvik-7" was successfully implanted into Barney Clark, who survived for 112 days. Previous attempts to implant artificial hearts pre-dating the development of the "Jarvik-7" were less successful, with patients only surviving for several hours or a few days. Since 1982, Jarvik hearts have been implanted in many patients with significantly longer survival rates. While Dr. Jarvik's success undoubtedly drew inspiration from and improved upon previous designs, it is for this accomplishment that he has achieved distinction as "inventor of the artificial heart."

Although we respectfully disagree with your challenge, we recognize the sensitivities of those who contributed to the development of a successful artificial heart and will, therefore, revise our description of Dr. Jarvik in the coming weeks.

Thank you again for raising your concerns.

Sincerely,

Marina Pearlman

Cc: Jeffrey B. Kindler
Peter C. Brandt
Marie-Caroline Saimpy
Michael A. Sussermun
C. Walt Johnston

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ABC News Transcript

SHOW: GOOD MORNING AMERICA 7:39 AM EST

January 16, 2008 Wednesday

2241 words

SHOULD DOCTORS BE TV PITCHMEN?;
CONGRESS PROBES ENDORSEMENT DEAL

DIANE SAWYER, ROBIN ROBERTS

DIANE SAWYER (NEW YORK, NY USA)

CONTENT: DOCTOR ROBERT JARVIK, LIPITOR, PFIZER, CONGRESS, REPRESENTATIVE JOHN DINGELL, KATIE WATSON

DIANE SAWYER (ABC NEWS)

(Off-camera) Well, as we said, a powerful congressional committee is now investigating a television ad for the world's most popular drug, asking questions of Pfizer, the creator of the drug, and also the man who's featured in the ad, Dr. Robert Jarvik.

CLIP FROM DOCTOR ROBERT JARVIK'S LIPITOR AD

DIANE SAWYER (ABC NEWS)

(Voiceover) Dr. Jarvik is going to join us in a moment to answer these questions. But first, let's take a look at the questions from Congress.

CLIP FROM DOCTOR ROBERT JARVIK'S LIPITOR AD

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

After my father had a heart attack, I devoted my life to studying the heart.

DIANE SAWYER (ABC NEWS)

(Voiceover) It is the biggest-selling drug in the world, and now the ads are under fire. In them, Dr. Robert Jarvik, inventor of the artificial heart, endorses the cholesterol-lowing drug Lipitor.

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

Lipitor is one of the most researched medicines. I'm glad I take Lipitor as a doctor and a dad.

GRAPHICS: SHOULD DOCTORS BE TV PITCHMEN?

GRAPHICS: CONGRESS PROBES ENDORSEMENT DEAL

DIANE SAWYER (ABC NEWS)

(Voiceover) But the powerful chairman of a congressional committee has launched an investigation.

REPRESENTATIVE JOHN DINGELL (DEMOCRAT

Is he entitled to give the appearances that he can prescribe prescription pharmaceuticals? I think the law of every single state and federal government would say, 'No, he's not, because he's not admitted to the practice of medicine in any state that we can find."

DIANE SAWYER (ABC NEWS)

(Voiceover) Dingell says Dr. Jarvik did go to medical school, but he's an inventor and not licensed to practice patient medicine nor to prescribe medicine to anyone. Congress has also asked for records proving Jarvik takes the medication as he states in the ads.

REPRESENTATIVE JOHN DINGELL (DEMOCRAT

We are looking to see whether, in fact, there is wrongdoing. But second of all, we're also looking to see whether or not the law needs to be changed to give us a better level of protection for the consumers.

CLIP FROM TV ADS

DIANE SAWYER (ABC NEWS)

(Voiceover) Drug companies spend $4.8 billion on ads, but only the US and New Zealand allowed direct advertising of prescription drugs to consumers.

GRAPHICS: $4.8 BILLION ON ADVERTISING

CLIP FROM SENATOR BOB DOLE'S VIAGRA AD

CLIP FROM SALLY FIELD'S BONIVA AD

DIANE SAWYER (ABC NEWS)

(Voiceover) Jarvik certainly isn't the first celebrity to appear in these ads. Senator Bob Dole, actress Sally Field have appeared in ads too. But critics ask, is a man who says he's a doctor crossing a different ethical line?

KATIE WATSON (MEDICAL HUMANITIES AND BIOETHICS PROGRAM

To have a celebrity physician associated with cardiac health telling me that I need Lipitor when it costs significantly more than a generic alternative that might be appropriate for me? That's a physician motivated by a paycheck, not by patient health.

DIANE SAWYER (ABC NEWS)

(Off-camera) A tough challenge there. Pfizer, the company behind Lipitor, is standing behind the ads.

GRAPHICS: STATEMENT FROM PFIZER

DIANE SAWYER (ABC NEWS)

(Voiceover) In the statement to ABC News, they say, 'Dr. Jarvik is a respected professional and heart expert." And that, quote, 'The advertising advises consumers to speak to their physicians about their heart health."

GRAPHICS: GMA EXCLUSIVE

DIANE SAWYER (ABC NEWS)

(Off-camera) So, what does - Dr. Jarvik say in response? He's with us this morning. Thank you for being us this morning.

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

Good morning. It's good to be here.

DIANE SAWYER (ABC NEWS)

(Off-camera) As we said, these are tough questions coming out of the congressional committee. Let me just address the first one. There seems to be an implication from Congressman Dingell that you are leaving the impression that you are a physician who can prescribe - medicine, who can see patients when, in fact, you cannot. Can you prescribe medication to patients?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

No. I am a medical scientist, not a practicing physician. You know what? It is, it, it is interesting, because it's hard for me to think of myself as public health enemy number one, you know? I don't see it that way. I think I'm there as the advocate of the public because preventive medicine is public health issue number one.

DIANE SAWYER (ABC NEWS)

(Off-camera) But let me ask you about a...

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

People need to avoid disease.

DIANE SAWYER (ABC NEWS)

(Off-camera) Let me ask you about a couple of questions raised in conjunction with that. They say that the distinction between a physician, who is licensed to prescribe medication, and a doctor, who graduated from medical school, is a distinction most people in the country don't make. And that you do leave the impression in the ad that you are a doctor, in the sense that lay people think of a doctor.

DIANE SAWYER (ABC NEWS)

(Voiceover) For instance, you say, 'I'm glad I take Lipitor as a doctor and a dad," at one point.

GRAPHICS: STATEMENT FROM DR. ROBERT JARVIK

DIANE SAWYER (ABC NEWS)

(Voiceover) And then, you say, 'Just because I'm a doctor doesn't mean I don't worry about my cholesterol." And you appear in a lab coat in another moment in that ad. Is that giving the wrong impression, the false impression?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

No, not at all. I think it's very upfront. I am a doctor. I have long experience with heart disease. I know how devastating it is. It's the number one health problem in the country. It's killing more people than anything. And the suffering from heart disease is enormous.

DIANE SAWYER (ABC NEWS)

(Off-camera) But the other thing we heard that ethicists say is that if you were acting as a physician doctor, that you would be talking about different things. You'd be talking about generic medicines, for instance, that could save people a lot of money and not endorsing a very comparatively expensive drug, and that you would be spending most of the ad talking about prevention and health.

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

You know, Lipitor is, is the most widely prescribed drug in the country. And for every prescription that's written, there's a doctor writing it. That's a huge vote of confidence in the importance for American health. And that, and there are, and there are other drugs in this class. It's not an issue about me. It's an issue about how do you get the public to understand that if they have a stroke, and if they could think, could I have gone back and taken a medication that could have avoided that, many people could.

DIANE SAWYER (ABC NEWS)

(Off-camera) So, you don't see anything here? You don't understand why these questions are being raised?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

No, I don't. I mean I think it's, it's really clearly an issue that our ad campaign with Pfizer is an educational campaign to teach the - nation that prevent...

DIANE SAWYER (ABC NEWS)

(Off-camera) But it's an ad, educational? It's an ad.

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

It's, yes, educational. It's important that people talk to their doctors.

DIANE SAWYER (ABC NEWS)

(Off-camera) What about generics? Why didn't you mention generics?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

I don't know. We have talked about generics in the ads. And I think that...

DIANE SAWYER (ABC NEWS)

(Off-camera) You have?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

Or maybe there's an ad that hasn't come out yet that you haven't seen. So we do - address those issues.

DIANE SAWYER (ABC NEWS)

(Off-camera) I wanna address a couple things that Congressman Dingell also raises. He says he wants to know, did you take Lipitor before you did the ad, because you talk about taking it?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

No. You know, that's very interesting because my father died of heart disease. I had high cholesterol. I exercise. I tried very hard to control my diet for a year. Numbers didn't change. I didn't, nothing move me to do it. I was fully aware of, of Lipitor for years. After I started doing the ads, about a month after, I said, you know, 'What about me?" And I saw my doctor, and he prescribed it for me.

DIANE SAWYER (ABC NEWS)

(Off-camera) He's also asking for all the records of how much you're paid.

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

Uh-huh.

DIANE SAWYER (ABC NEWS)

(Off-camera) And is your son paid as well? How much are you paid?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

I'm paid an amount that I think for, for a celebrity ad would be considered a lot by most people. But if you're...

DIANE SAWYER (ABC NEWS)

(Off-camera) You're gonna tell Congress how much?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

If, oh, sure. If you're talking about the amount of money that, say, professional athletes make for, for dealing with these things, I don't think it's, it's comparable to that. I think it's a, it's a lower scale than that. But people would think that it's a lot of money.

DIANE SAWYER (ABC NEWS)

(Off-camera) Let me ask you the philosophical question because, as we said, only the United States and New Zealand allow this direct marketing of prescription drugs to consumers. And a lot of people say this is distorting the medical system because doctors should make this decision, physicians should make this decision.

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

They do.

DIANE SAWYER (ABC NEWS)

(Off-camera) But does it bother you at all that there is all this ad money that might be applied, say, to research by the, by the drug companies? But does it bother you?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

Well, you know, I, if people wanna understand research, which in the pharmaceutical industry is extremely expensive. The advertising does a couple of things. It educates the public. It increases sales of those things that physicians believe are effective and that are appropriate for those patients and has the effect of increasing the amount of preventive medicine that's practiced in the country, which is a very good thing.

DIANE SAWYER (ABC NEWS)

(Off-camera) So, you think the ads increase preventive medicine in the country?

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

Absolutely. I think they do. I think that, that Lipitor is a preventive medicine. Most of the people taking it do not have symptoms of heart failure at that point. And they think, 'Oh, I'm okay." You know, you, you take two households. One household here with, say, a family of five or six people and another one next door. The members of one household say, you know, 'Heart disease is gonna get my neighbors and not me. We're gonna be okay." They feel they're gonna escape it. And they don't take action on their lives or talk to their doctors. They don't stop smoking. They don't control obesity. They don't do a lot of very important things for their health. And that's what it's all about, people understanding to take care of themselves.

DIANE SAWYER (ABC NEWS)

(Off-camera) All right. Dr. Jarvik, again, thanks so much for being with us. We'll be following this as Congress continues to probe. And thank you again for coming and answering the questions this morning.

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

You're welcome.

DIANE SAWYER (ABC NEWS)

(Off-camera) And congratulations on the Jarvik heart being in the Smithsonian, as I said.

DOCTOR ROBERT JARVIK (INVENTOR OF AN ARTIFICIAL HEART)

Thank you.

DIANE SAWYER (ABC NEWS)

(Off-camera) To weigh in, let us know what you think is fair, right, where do you stand? Go to ABCNEWS.com and tell us. We'll be back.

COMMERCIAL BREAK

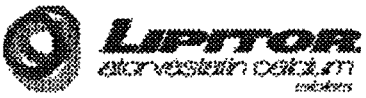
Declaration of use of LIPITOR by Dr. Robert Jarvik
Subject to Review by Company's Legal and Regulatory Departments

In consultation with my physician, I attest to my use of and preference for the Product as directed by my physician for high cholesterol. I agree that I shall immediately notify Pfizer if at any time I cease to use the Product.

Dr. ROBERT JARVIK

By: _____
Dr. Robert Jarvik

Date: June 22, 2006



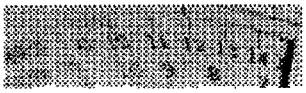
Pfizer Jarvik Advertising Campaign Diagnostic Research

Final Report

Prepared for:

Pfizer, Inc.





MAYA
GROUP
LTD

Prepared by:

Maya Group

November 2006

DETAILED FINDINGS

Overview

Overall reaction to the three Lipitor ads is quite favorable.

- As they watch the ads, about 60% of the Non-Treators indicate that they are more interested in asking their doctor about Lipitor. Few find anything objectionable or hard to believe to make them less interested.
- Many people agree that they like the ads and are interested in watching the entire executions.
- Whether they know a lot or a little about high cholesterol, they learn something new about the condition (can cause strokes in addition to heart attacks) and how Lipitor can help them (reducing bad cholesterol 39-60%).
- The spokesperson, Dr. Robert Jarvik, is well received as a medical expert. His personality comes across differently in the various ads, seeming most relatable in "Rowing" and most comfortable and engaging in "Human Body."
  - The doctor is described as authoritative, credible, intellectual, earnest, relaxed, regular, real, and convincing.

    "I like the Dr. Jarvik ads the best of all, because of his prominence, but my mind's constantly going to his status as a physician and what he's done, and how much is he getting paid to do that." (Non-Treator, Houston)

    "You see him as a real person rather than just a sterile doctor that comes out in a white lab coat." (Treator, Houston)

    "He's an expert. He invented the artificial heart. He's an expert in the cardiology. His resume, background speaks for itself. And I cannot conceive that the man would be out there selling a product with that type of background and integrity." (Non-Treator, Houston)

    "He said he's dedicated his life to care for heart. You know, working with the heart and caring for heart patients. He's made plenty of money. I don't think he's doing it for the money. He's doing it because he's found something that helps. If he's dedicated his life to it, he's made lots of money." (Non-Treator, Houston)
- Many participants believe that the intended audience for these ads is any consumers with high cholesterol. They do not feel that the ads are talking down to them, so they can connect with people who already possess a fair amount of knowledge about the condition or very little. They can relate to the material, as about three-quarters of respondents feel the ads are talking to someone like themselves.
- Most participants admit they are affected by seeing the ads. Many contend that they would talk to their doctor about Lipitor the next time they have a regularly scheduled doctor's appointment.

Mindy Goldberg Associates, Inc.
Mindy S. Goldberg, Ph.D.
13 Hidden Acres Drive
Voorhees, NJ 08043
856-772-9005
mgamindy@aol.com

Lipitor Generic Defense

Consumer Qualitative Research

MGA#0705

Submitted February 1, 2007

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Background

In 2007, there will be an increased focus and push behind generic statins, particularly generic Zocor, due to the availability of cheaper generics (driven by more manufacturers of generic Zocor, aka "multi-source")

Research indicates that managed care plans and a sub-segment of MDs will be more proactive in promoting and prescribing generic Zocor to patients

- From a plan perspective, the emphasis will be on encouraging current Lipitor patients to switch to generics, and incentivizing physicians to prescribe generics first line to new patients
- From the MD perspective, some doctors who traditionally would have prescribed Lipitor have suggested that they will ramp up their prescribing of generic Zocor to new patients

Objectives

The overall objectives of this research were to:

- Assess and refine several print (magazine/newspaper) and radio executions aimed at defending against generics, both switching to and starting on generic Zocor
- Understand the extent to which these executions communicate the main strategy, strengthen Users commitment to stay on Lipitor, or increase Non-Treaters' interest in Lipitor, in the face of generics
- Determine if the messaging and creative work in concert make a compelling case for Lipitor over generic options
- Evaluate the potential breakthrough ability of both the print and radio ads
- Understand the potential impact on consumer perceptions about the Lipitor brand
- Identify ways to enhance the advertising concepts

Methodology

20 in-depth interviews were conducted by Frances Darpino. Interviews lasted approximately 75 minutes

Interviews were conducted in New York City, Houston TX and Los Angeles

Respondents consisted of:

- 13 Lipitor Users, a mix of consumer segments
- 7 Diagnosed Non-Treaters, consisting of 4 Prevention Believers and 3 Sick and Overwhelmed

Respondents ranged in age from 35-67, a mix by gender, ethnicity, and socio-economic status

Research Caveat

- Research findings are based upon qualitative exploration of topics
- As is customary with all qualitative research, it should be stated that findings generated through a limited number of focus groups and in-depth interviews may not be generalized with statistical confidence to the population at large
- Rather, findings should be viewed as hypotheses, providing a thorough understanding of how and why respondents feel and act as they do

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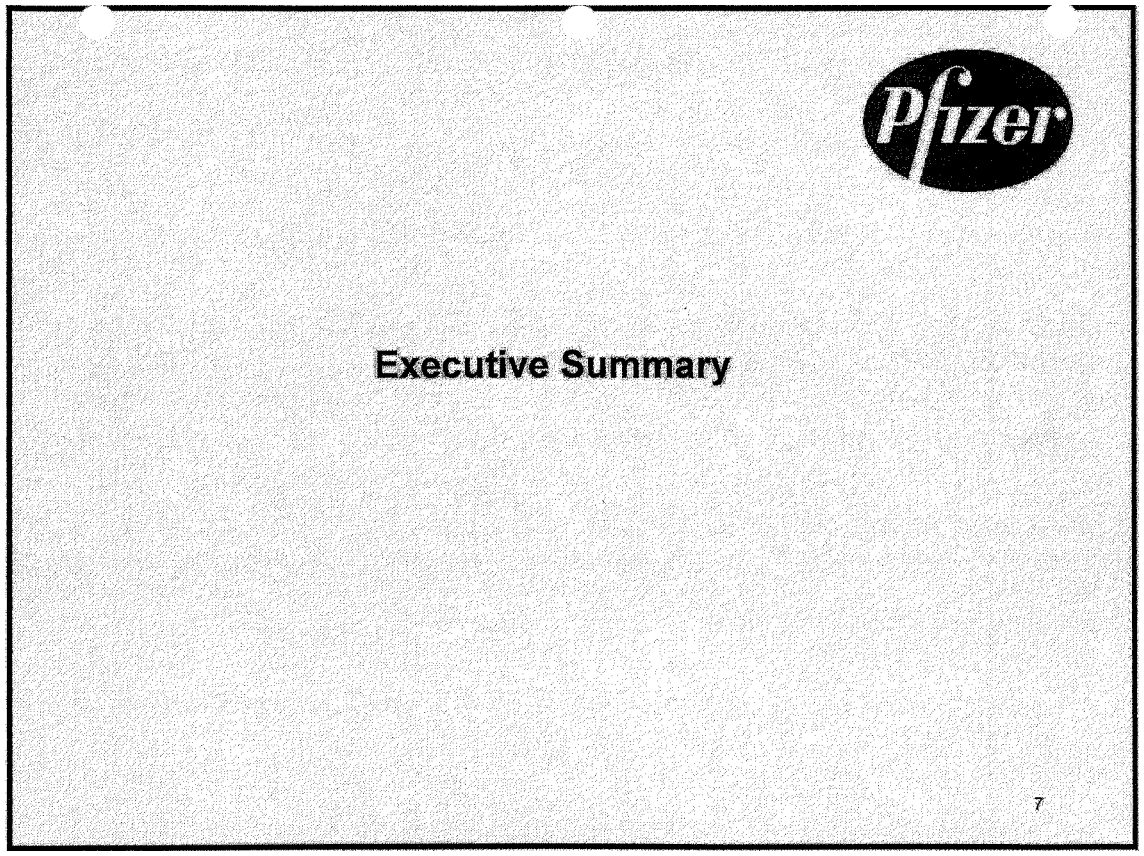
Executive Summary
7

Executive Summary - Lipitor Generic Defense

- **Dr. Jarvik is an asset in both the print and radio ads**. He is viewed as an appropriate spokesperson, an *"expert"* on heart health, *"knows the heart," "not a paid actor, not fly-by-night."* Dr. Jarvik helps to capture attention, adds to the credibility of Lipitor, and slightly elevates the impact of the ads in terms of generic defense. Communication that he takes Lipitor tends to promote identification with the brand
- **The print executions do not seem to be highly persuasive as a generic defense; however, there may be a viable opportunity for the print and radio ads to strengthen Users' commitment to stay on Lipitor and increase Non-Treaters' interest in the brand if there are clearer, stronger statements in key areas, such as CV benefits versus generics, and Lipitor LDL reduction superiority to Zocor**
  - Several messages are compelling and have some potential breakthrough; however, **without stronger and somewhat more differentiating statements, the ads may be perceived as broad-based Lipitor brand advertising**
- **In addition to stronger statements, it seems worthwhile to consider combined rather than single-focus messaging, both in print and radio ads**. Message combinations could be more compelling and persuasive, and aid in differentiating Lipitor versus generics
- **In the print ads, CV benefits (H) resonates the most, in part due to the visual impact of the heart graphic combined with Dr. Jarvik and the headline**. As presented, the creative seems to be directionally correct in terms of strengthening Lipitor in the face of generics

Executive Summary - Lipitor Generic Defense

- Suggested improvements for **CV benefits (H)**
  - **Lead off with a clearer, stronger CV statement** to clearly convey Lipitor has risk reduction data that sets it apart from generic cholesterol-lowering medication
  - **Strive to develop and obtain approval for a stronger, more targeted generic message** to replace the 1st bullet, "misperceptions," "no generic substitute." One approach is to focus on Lipitor superior LDL reductions. Ideally, develop a stronger, more compelling statement about generic differences
- **Research (R) is the most differentiating print message in terms of the overall Lipitor brand.** Four hundred ongoing and clinical trials is impressive and provides some reassurance about safety and efficacy; however, the creative seems to need additional information to support generic defense
  - **More significant LDL lowering than Zocor may be a persuasive and worthwhile support point as another reason why Dr. Jarvik takes Lipitor.** The reference to Zocor may heighten awareness of the generic defense message. Communicating that scientific research is one of the reasons why Dr. Jarvik takes Lipitor does not appear to be enough
  - **Strive to state more clearly and forcefully that Lipitor has more research than Zocor and other generics.** In (S), the line that reads "Lipitor has been more extensively studied than Zocor or any other generic cholesterol-lowering medicine," may be a clearer and more persuasive communication than (R)

Executive Summary - Lipitor Generic Defense

- Key learning from **(N) and (L) seems to be the relevance of superior LDL reduction to Treaters and Non-Treaters;** however, a single-minded LDL message may not be a strong enough defense versus Zocor
  - The LDL message may be more effective as a **support point,** especially in light of competitive brand lipid-lowering data
  - The **39-60% numbers are eye-catching and compelling**. Explore punching up the numbers, using more color or a graphic
  - Learning from the (N) and (L) executions suggests the importance of **showing a picture of Dr. Jarvik** for its stopping power, and **clarifying that he is making the claim** in the headline
  - **Stronger, clearer communication of the 2nd bullet is needed**. Current language, "Zocor is available in a generic form, but Zocor is still less effective than Lipitor," is weak and confusing. If possible, use language that clearly conveys "Zocor is less effective than Lipitor," or "generic Zocor is less effective than Lipitor"

Executive Summary - Lipitor Generic Defense

- The **no generic substitute (S) message is polarizing** and does not seem worthwhile to pursue
  - **Respondents who react favorably tend to focus on the multiple facts about Lipitor**, i.e., more significant LDL lowering than Zocor, the percentage, and more extensively studied than Zocor or any other generic cholesterol-lowering medicine
  - **Respondents who are lukewarm tend to react negatively to the headline, and/or the *"boring"* recitation of facts**
- **Conveying "no generic substitute for Lipitor" in this context does not seem to be helpful or educational** in a way that would strengthen the Lipitor defense
- **Explore a stronger "no generic" statement** to help set Lipitor apart from generics
  - Determine if there is any information that can be used to distinguish Lipitor from generics. Suggest that the Lipitor molecule is unique, or there are differences in side effect profiles and drug interactions, or there are quality variations between Lipitor and generics, or any other elements that could convey specific differences between branded Lipitor and generics and/or create doubts about generic alternatives
- The **tagline, "could you be doing more... with Lipitor" continues to be interpreted primarily as a call-to-action to take Lipitor**, or an opportunity to have a more active lifestyle and overall improved health by taking Lipitor

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Executive Summary - Lipitor Generic Defense

- **The radio ads seem to be slightly more breakthrough than the print ads, especially when Dr. Jarvik's name and credentials are more readily discernible at the start of the ad, and there is clear communication that he takes Lipitor**
  - For many respondents, **Dr. Jarvik grabs attention** and draws them into the ad
  - Dr. Jarvik's **personal usage** of Lipitor personalizes the endorsement and enhances the credibility of the Lipitor message
  - The **continuity with TV commercials and print ads is a benefit and could help to strengthen Lipitor brand presence**
- **Research focus, (M), i.e., more studied, and 400 ongoing and completed clinical trials, seems to be the most attention grabbing element of the ads**, and resonates with both Treaters and Non-Treaters
  - However, research data alone does not appear to be strong enough to defend Lipitor versus generic Zocor
- **For any radio ad, consider combined messages to better address the challenge of defending Lipitor versus generic Zocor**
  - **One approach is to consider including a straightforward LDL reduction message as part of any radio ad**, such as, "in a clinical study, Lipitor...atorvastatin calcium...lowered cholesterol significantly more than Zocor." The LDL message is clear and easy to understand, and goes head-to-head vs. Zocor in an *"informative"* and *"objective way,"* without bashing

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Executive Summary - Lipitor Generic Defense

- Examples of **combined messages for radio**
  - **LDL reduction is a good fit with a research focus (M).** Most respondents relate to the "factual, informative" tone of the research ad, and feel it provides reassurance about efficacy and safety
  - Similarly, it may be worthwhile to communicate **superior LDL reduction as part of a refined CV benefits message (C).** The CV benefits spot seems to warrant consideration if the CV message is dialed up and clarified. Communication of CV benefits and risk factors has potential to grab attention. CV benefits is an important, relevant message that is not well understood or differentiating as written
- The **drawbacks of switching ad (G) does not seem to merit further consideration.** The message is not compelling, and the switcher target excludes Non-Treaters who may consider Lipitor
- After respondents reviewed all of the ads, they were asked to read and react to a managed care letter. Learning based on the small sample size and limited time:
  - Some respondents, especially Treaters, and those who had negative perceptions of Zocor and/or generics, would toss the letter, citing their satisfaction with Lipitor, and/or distrust of managed care, *"they're not looking out for my best interest"*
  - However, many respondents, especially Non-Treaters, would at least ask their doctor about it, *"are the ingredients the same," "what is better for me"*
  - The co-pay difference would be one tipping point that could influence likelihood to switch, *"it depends on the price difference"*

Executive Summary - Lipitor Generic Defense

- **At the conclusion of the interview, respondents were asked to cite the three main reasons why they would stay with/consider Lipitor in light of the materials presented**
  - **Some respondents cite reduced risk of heart attack, stroke and heart surgery as a key factor**, especially if they believe that generics do not have similar data
    - However, other respondents believe that risk reduction is a class effect associated with lowering cholesterol, and the message as stated does not clearly distinguish Lipitor from other cholesterol-lowering medications. The message as stated does not distinguish Lipitor from generics
  - **Research resonates**. "Tested more than others" conveys both safety and efficacy. Research is typically viewed as a more differentiating claim
  - **Lowers LDL more effectively than Zocor is meaningful**, even though the ads do not quantify the difference. It seems acceptable (although it is not as persuasive) to communicate the Lipitor percentage without giving specific information about Zocor
  - **Dr. Jarvik's role as a spokesperson is mildly persuasive to some respondents**, *"he has firsthand experience with all of the drugs, weighed the pros and cons, and he chose Lipitor over the generic"*

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Note: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUBMITTED: 07/06/06

2. LABEL REVIEW NO. (Biologics): 204373 Yarvik

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 2008
See OMB Statement on Reverse of Part1

3. NDA/ANDA/AADA OR BLA/PLA/PMA
Number: NDA 20-702
Single product X Multiple products

For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice, and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.

4. PROPRIETARY NAME	5. ESTABLISHED NAME	6. PACKAGE INSERT DATE and ID NO. (Latest final printed labeling)	7. MANUFACTURER NAME:
Lipitor	Atorvastatin Calcium Tablets Prod. Code No.	9/05 LAB-0021-9.0	License No. (Biologics)

FDA/CBER USE ONLY

REVIEWED BY:	DATE	RETURNED BY:	DATE

8. ADVERTISEMENT / PROMOTIONAL LABELING MATERIALS

Please check one or both: Professional X Consumer

Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:
CTL	07/17/06	LP273987-B – Lipitor Live Operator "Dr. Jarvik" FAQ Script		
CAD	07/12/06	LP275952-A – Lipitor Print Ad (7" x 10")		

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Robert B. Clark,
Vice-President, US Regulatory

10. SIGNATURE OF RESPONSIBLE OFFICIAL
[signature] for RB Clark

11. APPLICANT'S RETURN ADDRESS
Pfizer Inc.
Regulatory Affairs
235 East 42nd Street
New York, New York, 10017

RECEIVED
JUL 07 2006
CDER White Oak DR2

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO. (212) 573-3412
b. FAX NO. (212) 672-7807

13. BIOLOGICAL PRODUCTS: (Check one)
☐ Part I/Draft ☐ Part II/Final

FORM FDA 2253 (6/05) PREVIOUS EDITION IS OBSOLETE. PSC Media Arts (301) 443-1090 EF

PFIZER
LIPITOR Branded
Lipitor Live Operator "Dr. Jarvik" FAQs
Accessed via 1-888-LIPITOR
PE #LP273987 - B

The Lipitor Live Operator Dr. Jarvik FAQs (LP273987- B) is a companion to the Lipitor Live Operator Script (LP273978). Consumers reach a Live Operator by dialing 1-888-LIPITOR and selecting a "Live Operator Prompt". Once connected with the Live Operator they are given the opportunity to ask question(s) about Lipitor print and TV ads, featuring Dr. Robert Jarvik, whereby the Operator accesses the Dr. Jarvik FAQs.

Proprietary and Confidential

LIPITOR
Dr. Jarvik
Frequently Asked Questions
PE# 273987 - B

Subject Code	Response Code	Question	Response
JARVIK	LDRJ01	**Who is Dr. Robert Jarvik?**	Dr. Jarvik is a medical doctor and the inventor of the first permanent artificial heart used for people waiting for a heart transplant. He was motivated to invent the heart after his father, also a medical doctor, died of heart disease.
JARVIK	LDRJ02	**Is Dr. Jarvik a real doctor? What are his credentials?**	Yes. Dr. Jarvik is a medical doctor with a degree from the University of Utah College of Medicine. He also has a Master's Degree in Biomechanics from New York University, and a degree in Zoology from Syracuse University.
JARVIK	LDRJ03	**Does Dr. Jarvik see patients and prescribe medication like LIPITOR?**	No, he does not see patients. Dr. Jarvik is currently focused on medical research and developing innovative health care products for patients. He is not a practicing doctor.
JARVIK	LDRJ04	**Why is Dr. Jarvik doing advertising commercials for LIPITOR?**	Given his experience with heart disease, Dr. Jarvik recognizes that LIPITOR, along with a healthy diet and exercise, can help people significantly lower their high cholesterol. High cholesterol, family history, high blood pressure, age, low LDL or smoking are risk factors for heart disease and stroke.
JARVIK	LDRJ05	**What does Dr. Jarvik know about heart disease?**	Dr. Jarvik is a medical doctor involved in patient research. His father, also a medical doctor, died of heart disease. His father's death motivated him to invent the first permanent artificial heart in 1982.
JARVIK	LDRJ06	**Is Dr. Jarvik being paid for being in the commercial?**	Yes, Dr. Jarvik is compensated for his time.

LIPITOR
Dr. Jarvik
Frequently Asked Questions
PE# 273987 - B

Subject Code	Response Code	Question	Response
JARVIK	LDRJ07	**What is the history of the Jarvik heart?**	In 1982, the Jarvik-7, the first artificial heart invented by Dr. Jarvik, was implanted successfully into Barney Clark. Clark lived for 11 days with the artificial heart. A smaller, improved version of the Jarvik 7 was then designed. Since it has become available, it has sustained hundreds of patients until they were able to get a human heart transplant.
JARVIK	LDRJ08	**I remember reading some negative news articles about Dr. Jarvik. Didn't his artificial heart fail?**	In 1982, the Jarvik-7, the first artificial heart invented by Dr. Jarvik, was implanted successfully into Barney Clark. Clark lived for 11 days with the artificial heart. A smaller, improved version of the Jarvik 7 was then designed to sustain hundreds of patients until they were able to get a human heart transplant.
JARVIK	LDRJ09	**How can I learn more about the Jarvik heart?**	You can go to the Jarvik heart website at www.jarvikheart.com to learn more. This is not a Pfizer website. Pfizer takes no responsibility for the content of the website.

American Medical Association
POLICY

H-105.988

Direct-to-Consumer (DTC) Advertising of Prescription Drugs and Implantable Devices

It is the policy of our AMA:

1. That our AMA considers acceptable only those product-specific DTC advertisements that satisfy the following guidelines:

(a) The advertisement should be indication-specific and enhance consumer education about both the drug or implantable medical device, and the disease, disorder, or condition for which the drug or device is used.

(b) In addition to creating awareness about a drug or implantable medical device for the treatment or prevention of a disease, disorder, or condition, the advertisement should convey a clear, accurate and responsible health education message by providing objective information about the benefits and risks of the drug or implantable medical device for a given indication. Information about benefits should reflect the true efficacy of the drug or implantable medical device as determined by clinical trials that resulted in the drug's or device's approval for marketing.

(c) The advertisement should clearly indicate that the product is a prescription drug or implantable medical device to distinguish such advertising from other advertising for non-prescription products.

(d) The advertisement should not encourage self-diagnosis and self-treatment, but should refer patients to their physicians for more information. A statement, such as "Your physician may recommend other appropriate treatments," is recommended.

(e) The advertisement should exhibit fair balance between benefit and risk information when discussing the use of the drug or implantable medical device product for the disease, disorder, or condition. The amount of time or space devoted to benefit and risk information, as well as its cognitive accessibility, should be comparable.

(f) The advertisement should present information about warnings, precautions, and potential adverse reactions associated with the drug or implantable medical device product in a manner (e.g., at a reading grade level) such that it will be understood by a majority of consumers, without distraction of content, and will help facilitate communication between physician and patient.

(g) The advertisement should not make comparative claims for the product versus other prescription drug or implantable medical device products; however, the advertisement should include information about the availability of alternative non-drug or non-operative management options such as diet and lifestyle changes, where appropriate, for the disease, disorder, or condition.

(h) In general, product-specific DTC advertisements should not use an actor to portray a health care professional who promotes the drug or implantable medical device product, because this portrayal may be misleading and deceptive. If actors portray health care professionals in DTC advertisements, a disclaimer should be prominently displayed.

(i) The use of actual health care professionals, either practicing or retired, in DTC to endorse a specific drug or implantable medical device product is discouraged but if utilized, the advertisement must include a clearly visible disclaimer that the health care professional is compensated for the endorsement.

(j) The advertisement should be targeted for placement in print, broadcast, or other electronic media so as to avoid audiences that are not age appropriate for the messages involved.

(k) In addition to the above, the advertisement must comply with all other applicable Food and Drug Administration (FDA) regulations, policies and guidelines.

2. That our AMA opposes product-specific DTC advertisements, regardless of medium, that do not follow the above AMA guidelines.

3. That the FDA review and pre-approve all DTC advertisements for prescription drug or implantable medical device products before pharmaceutical and medical device manufacturers (sponsors) run the ads, both to ensure compliance with federal regulations and consistency with FDA-approved labeling for the drug or implantable medical device product.

4. That the Congress provide sufficient funding to the FDA, either through direct appropriations or through prescription drug or implantable medical device user fees, to ensure effective regulation of DTC.

5. That DTC advertisements for newly approved prescription drug or implantable medical device products not be run until physicians have been appropriately educated about the drug or implantable medical device. The time interval for this moratorium on DTC for newly approved drugs or implantable medical devices should be determined by the FDA, in negotiations with the drug or medical device product's sponsor, at the time of drug or implantable medical device approval. The length of the moratorium may vary from drug to drug and device to device depending on various factors, such as: the innovative nature of the drug or implantable medical device; the severity of the disease that the drug or implantable medical device is intended to treat; the availability of alternative therapies; and the intensity and timeliness of the education about the drug or implantable medical device for physicians who are most likely to prescribe it.

6. That our AMA opposes any manufacturer (drug or device sponsor) incentive programs for physician prescribing and pharmacist dispensing that are run concurrently with DTC advertisements.

7. That our AMA encourages the FDA, other appropriate federal agencies, and the pharmaceutical and medical device industries to conduct or fund research on the effect of DTC, focusing on its impact on the patient-physician relationship as well as overall health outcomes and cost benefit analyses; research results should be available to the public.

8. That our AMA supports the concept that when companies engage in DTC, they assume an increased responsibility for the informational content and an increased duty to warn consumers, and they may lose an element of protection normally accorded under the learned intermediary doctrine.

9. That our AMA encourages physicians to be familiar with the above AMA guidelines for product-specific DTC and with the Council on Ethical and Judicial Affairs (CEJA) Ethical Opinion E-5.015 and to adhere to the ethical guidance provided in that Opinion.

10. That the Congress should request the Agency for Healthcare Research and Quality (AHRQ) to perform periodic evidence-based reviews of DTC in the United States to determine the impact of DTC on health outcomes and the public health. If DTC is found to have a negative impact on health outcomes and is detrimental to the public health, the Congress should consider enacting legislation to increase DTC regulation or, if necessary, to prohibit DTC in some or all media. In such legislation, every effort should be made to not violate protections on commercial speech, as provided by the First Amendment to the U.S. Constitution.

11. That our AMA continues to monitor DTC, including new research findings, and work with the FDA and the pharmaceutical and medical device industries to make policy changes regarding DTC, as necessary.

12. That our AMA supports "help-seeking" or "disease awareness" advertisements (i.e., advertisements that discuss a disease, disorder, or condition and advise consumers to see their physicians, but do not mention a drug or implantable medical device or other medical product and are not regulated by the FDA). (BOT Rep. 38 and Sub. Res. 513, A-99; Reaffirmed: CMS Rep. 9, Amended: Res. 509, and Reaffirmation I-99; Appended & Reaffirmed: Sub. Res. 503, A-01; Reaffirmed: Res. 522, A-02; Reaffirmed: Res. 914, I-02; Reaffirmed: Sub. Res. 504, A-03; Reaffirmation A-04; Reaffirmation A-05; Modified: BOT Rep. 9, A-06)

Amchin, Wayne

From: Amchin, Wayne
Sent: Monday, December 31, 2007 1:48 PM
To: Amchin, Wayne; Direct-to-Consumer Advertising-PDUFA
Subject: FW: Lipitor DTC User Fee submission-Doctors for Lipitor: Dr. Kloner, "PDUFA-MACMIS" # P50146

From: Browne, Ursula [mailto:ursula.browne@Pfizer.com]
Sent: Thursday, December 27, 2007 2:47 PM
To: Vaswani, Sangeeta; Direct-to-Consumer Advertising-PDUFA; Amchin, Wayne
Subject: RE: Lipitor DTC User Fee submission-Doctors for Lipitor: Dr. Kloner, "PDUFA-MACMIS" # P50146

Dear Ms. Vaswani,

Thank you for your reply. As noted in our response, Dr. Kloner is one of many physicians under consideration for the proposed "Doctors For Lipitor" campaign. Should Pfizer move forward with this television ad, proper verification of the selected physician's credentials and actual Lipitor use will be provided as per your request. The verification is necessary not only to fulfill your request, but also to adhere with FTC guidelines, as networks will also wish to verify the authenticity of the spokesperson being used. The verification that will be provided will be consistent with the affidavit provided by Dr. Robert Jarvik, current spokesperson for Lipitor. Such an affidavit will not be secured until the ad script and visuals are finalized and casting/production decisions are made.

Pfizer is not aware of established criteria that constitute requirements for a submission to be deemed complete and will take this into consideration for future submissions. However, the provision of verification of physician credentials should not preclude the evaluation of the promotional claims proposed in the ad, whether voiced by Dr. Kloner, or another physician endorsing Lipitor. Pfizer respectfully requests the review commence, and that DDMAC note this observation in their advisory comments. We welcome the opportunity to discuss this further, if needed.

Many thanks,
Ursula Browne

From: Vaswani, Sangeeta [mailto:sangeeta.vaswani@fda.hhs.gov]
Sent: Wednesday, December 26, 2007 4:12 PM
To: Browne, Ursula
Subject: FW: Lipitor DTC User Fee submission-Doctors for Lipitor: Dr. Kloner, "PDUFA-MACMIS" # P50146

Hi Ursula,

Katlin and I just left you a voicemail letting you know that the amendment to your Lipitor TV ad submission is incomplete and not reviewable. Please provide 10 copies each of the following:

- Verification that Dr. Richard Kloner is a cardiologist and Director of Research Heart Institute and is not a model or actor.
- Verification that Dr. Richard Kloner is an actual Lipitor patient and is not a model or actor

We note that it is your belief and understanding that Dr. Kloner is a cardiologist, Lipitor patient, and Director of

Research at the Heart Institute. However, we still require formal verification for this review. Please feel free to contact me at 301-796-1200 or Katlin at 301-796-2173 if you need any additional information.

Regards,

Sangeeta Vaswani, Pharm.D.
Consumer Safety Officer
Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
301-796-1200 (phone)
301-796-9877 (fax)

From: Amchin, Wayne
Sent: Tuesday, December 18, 2007 5:34 PM
To: Kiester, Marci; Vaswani, Sangeeta
Subject: FW: Lipitor DTC User Fee submission-Doctors for Lipitor: Dr. Kloner, "PDUFA-MACMIS" # P50146

From: Amchin, Wayne **On Behalf Of** Direct-to-Consumer Advertising-PDUFA
Sent: Tuesday, December 18, 2007 5:34 PM
To: 'Browne, Ursula'
Cc: Direct-to-Consumer Advertising-PDUFA
Subject: Lipitor DTC User Fee submission-Doctors for Lipitor: Dr. Kloner, "PDUFA-MACMIS" # P50146

Ursula Browne
Director
US Regulatory Affairs
Pfizer Global Pharmaceuticals
235 East 42nd Street
New York, NY 10017-5755

Ursula:

We received this DTC user fee ad, and we have determined that the submission is incomplete and not reviewable. To make this submission complete and reviewable, please provide 10 copies each of the following:

- Verification that Dr. Richard Kloner is a cardiologist and Director of Research Heart Institute and is not a model or actor.
- Verification that Dr. Richard Kloner is an actual Lipitor patient and is not a model or actor.
- Reference #1 states "The reference for this claim, spreadsheets listing the 410 ongoing or completed Lipitor clinical trials, was submitted to DDMAC by email on December 8, 2006 and as a hard copy on December 18, 2006." We need the spreadsheets to be submitted as part of this submission as well. Each submission should be complete as a stand-alone submission and should not rely on references previously submitted to DDMAC as part of a separate submission.

Wayne Amchin
DDMAC Project Manager
301-796-1200
dtcp@fda.hhs.gov

"MMS <secure.pfizer.com>" made the following
annotations on 12/27/07, 14:46:38

LEGAL NOTICE:

Unless expressly stated otherwise, this message is confidential and may be privilege

==========

Legal Notice

==========

"EMF <fda.hhs.gov>" made the following annotations.

This message was sent from Pfizer Corporation across the internet in encrypted forma

==========

Vendor List

"Father" Videomatic

Pomann Sound	$260.10
Continuity Graphics	5,901.00
Visual Sound Group	257.93.

6 -:60 Animatics: "Jarvik Forum", "Forum/Offer", "Maze", "Comes A Day", "Worth It" and "No Substitute"

Continuity Graphics	$95,140.00
Phantom Casting & Audio	10,675.00
Talent Partners	4,837.53

4-:60 Animatics: "Leaves", "Pills", "Antibiotics" and "Monitor"

Phantom Audio	$5,150.00
Talent Partners	1,110.56
Visual Sound Group	85.42

Awaiting Continuity Graphics Invoice

6-:60 Animatics: "Dr. Mosca", "Dr. Kloner", "On the One", "Lend My Name","Professor", "Treadmill"

Phantom Audio	$11,612.50
Continuity Graphics	180,460.00
Visual Sound Group	777.56
Talent Partners	6,536.98

Worldwide Public Affairs & Policy
Pfizer Inc
325 7th Street, NW Suite 1200
Washington, DC 20004
Tel 202 783 7070 Fax 202 347 2044
Email anthony.principi@pfizer.com



Anthony J. Principi
Senior Vice President
Federal Government Relations

February 25, 2008

The Honorable John Dingell
Chairman
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Dingell and Chairman Stupak:

Thank you for your January 7, 2008, letter expressing concern that consumers may misinterpret Lipitor advertisements that utilize Dr. Robert Jarvik. Pfizer is announcing today that it is voluntarily withdrawing Lipitor advertising and promotion featuring Dr. Jarvik, and is committed to ensuring greater clarity in the roles and responsibilities of its spokespeople in its consumer advertising and promotion.

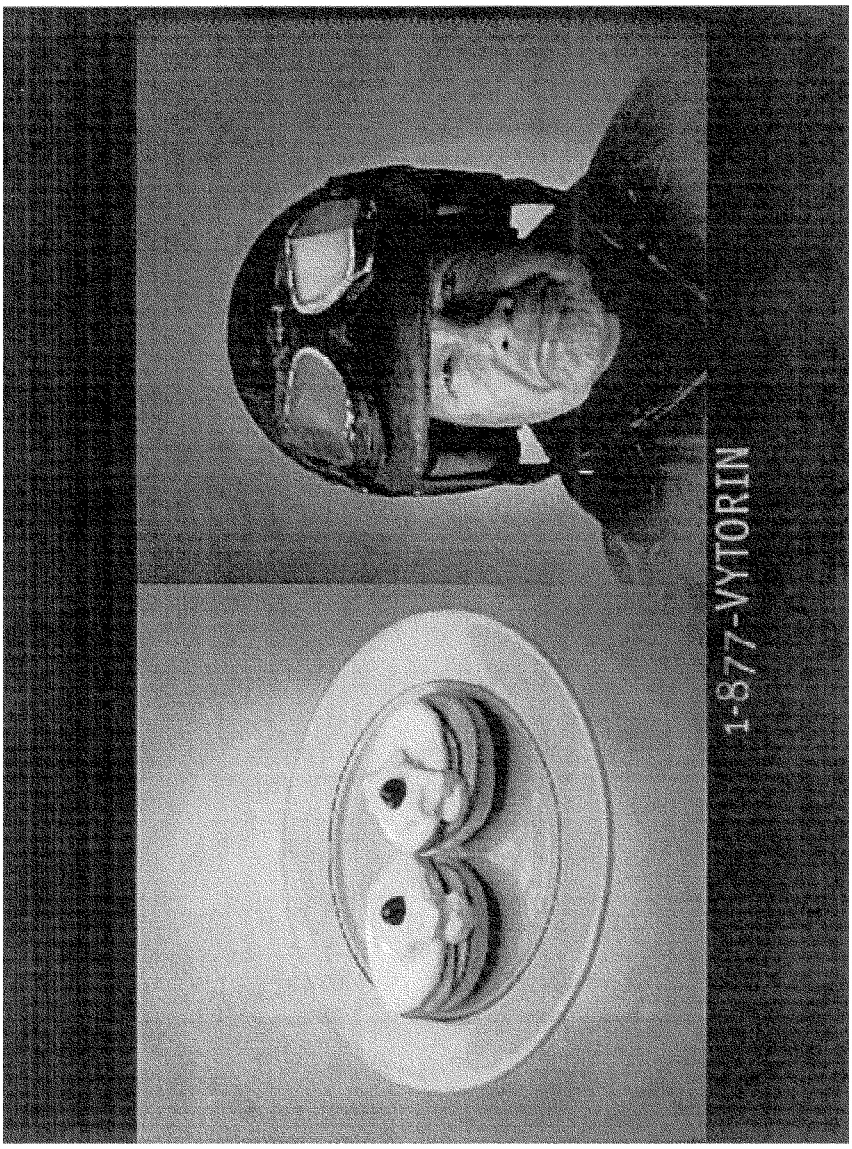
Unfortunately, the way Dr. Jarvik was presented in these ads has created misimpressions and distractions from our primary goal of encouraging patient and physician dialogue on the leading cause of death in the world: cardiovascular disease. We regret this. Going forward, Pfizer is committed to greater clarity in our advertising regarding use of spokespeople and their relationship with Pfizer.

Please do not hesitate to contact me if you have any questions.

Sincerely,

Anthony J. Principi

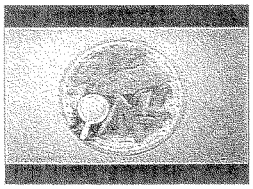
cc: The Honorable John Shimkus
The Honorable Joe Barton


1-877-WYTORIN

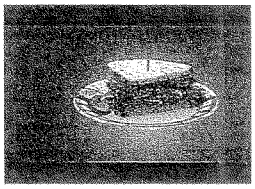
DDB

20550086(1)

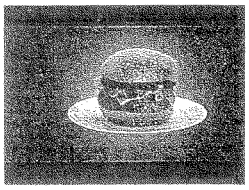
VYTORIN "Cholesterol Portraits" - Non-New :60



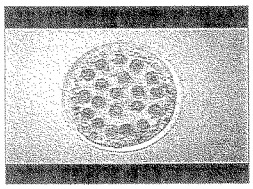
1.



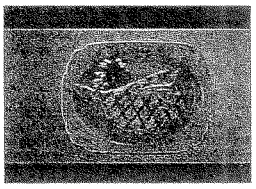
2.



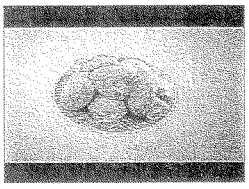
3. Cholesterol.



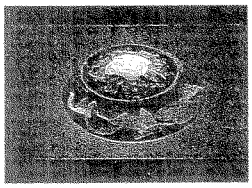
4. It comes



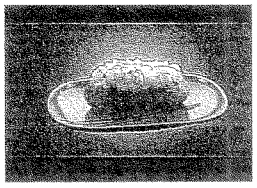
5. grilled,



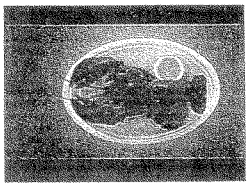
6. fried,



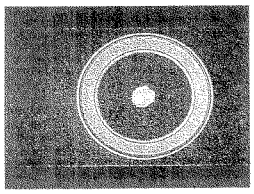
7. slow cooked,



8. twice baked,



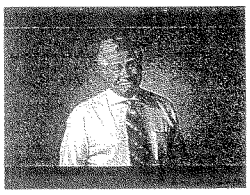
9. poached,



10. and pureed.



11. But, it also comes from mom,



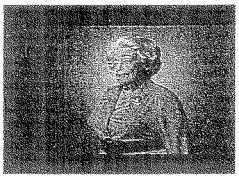
12. dad,

MSPP 165548.05

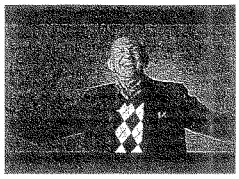
20550086(1)

DDB

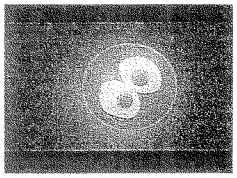
VYTORIN "Cholesterol Portraits" - Non-New :60



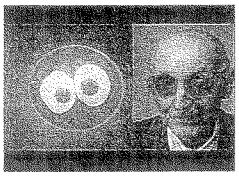
13. Grandma Ethel,



14. and Grandpa Sam.



15. Your cholesterol doesn't just come from food.



16. It also has a lot to do with family history.

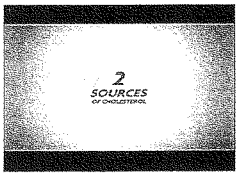


17. Ask your doctor about Vytorin.

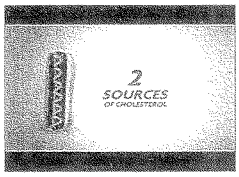
SUPER: Available by prescription only



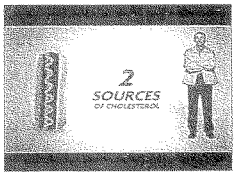
18. When diet and exercise aren't enough, adding Vytorin can help.



19. Vytorin treats the 2 sources of cholesterol–



20. cholesterol from food and



21. the cholesterol your body makes naturally based on family history.

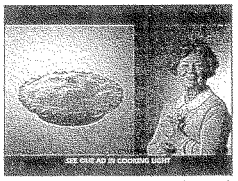


22. Vytorin lowers bad cholesterol



23. 45%-60%.

SUPER: Average effect depending on dose



24. Vytorin is not for everyone, including people with liver problems, women who are nursing, pregnant, or may become pregnant.

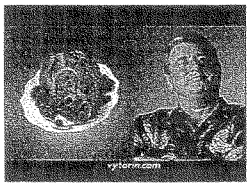
SUPER: See our ad in Cooking Light

MSPP 165548.06

DDB

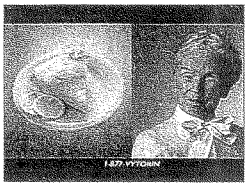
20550086(1)

VYTORIN "Cholesterol Portraits" - Non-New :60



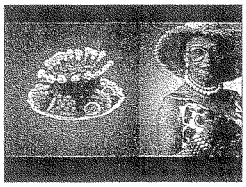
25. Unexplained muscle pain or weakness could be a sign of a rare but serious side effect.

SUPER: Vytorin.com



26. Vytorin may interact with other medicines or certain foods, increasing your risk of getting this serious side effect.

SUPER: 1-877-VYTORIN

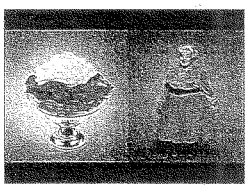


27. Simple blood tests are needed to check for liver problems.



28. Ask your doctor about Vytorin.

SUPER: Ask your doctor



29. Your cholesterol comes from 2 sources.



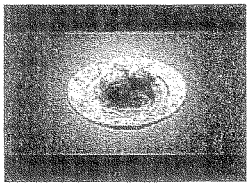
30. Treat them both with Vytorin

MSPP 165548.07

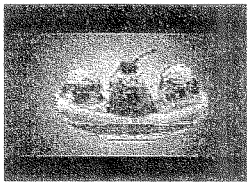
DDB

20550813(1)

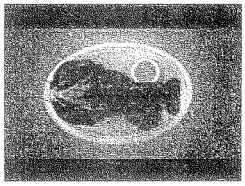
VYTORIN "Cholesterol Portraits 2" Rev. :60



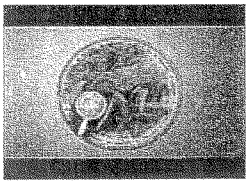
1.



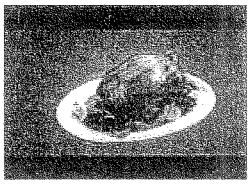
2. Cholesterol. It comes



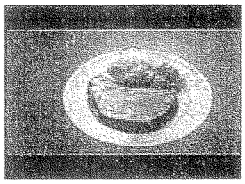
3. buttered,



4. battered,



5. basted



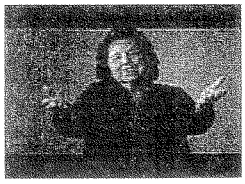
6. and roasted.



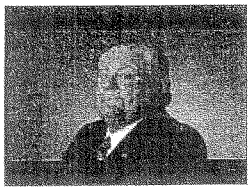
7. But, it also comes from mom,



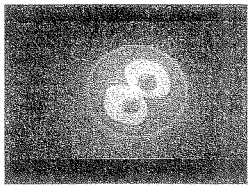
8. dad,



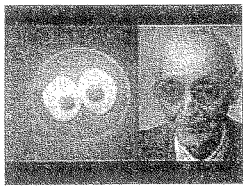
9. Grandma Rose



10. and Grandpa Joe.



11. Your cholesterol doesn't just come from food.



12. It also has a lot to do with family history.

MSPP 165548.08

DDB

20550813(1)

VYTORIN "Cholesterol Portraits 2" Rev. :60



13. Ask your doctor about Vytorin.

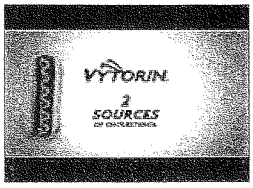
SUPER: Available by prescription only



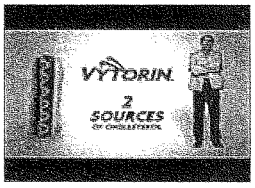
14. A healthy diet is important, but when it's not enough adding Vytorin can help.



15. Vytorin treats the 2 sources of cholesterol–



16. food



17. and what your body makes naturally based on family history.



18. Vytorin lowers bad cholesterol



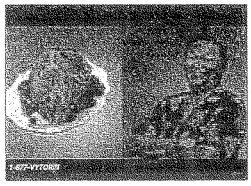
19. 45%-60%.

SUPER: Average effect depending on dose



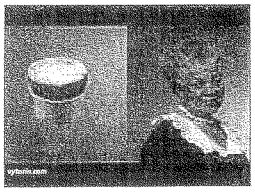
20. Vytorin is not for everyone, including people with liver problems, women who are nursing, pregnant, or may become pregnant.

SUPER: See our ad in Cooking Light



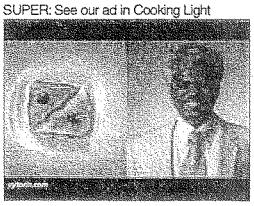
21. Unexplained muscle pain or weakness could be a sign of a rare but serious side effect.

SUPER: 1-877-VYTORIN



22. Vytorin may interact with other medicines or certain foods, increasing your risk of getting this serious side effect.

SUPER: vytorin.com



23. Simple blood tests are needed to check for liver problems.

SUPER: vytorin.com



24. Continue to follow a healthy diet and ask your doctor about adding Vytorin.

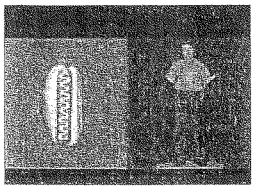
SUPER: Ask your doctor

MSPP 165548.09

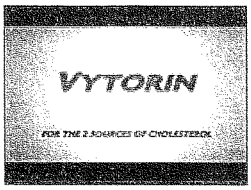
DDB

20550813(1)

VYTORIN "Cholesterol Portraits 2" Rev. :60



25. For the 2 sources of cholesterol-



26. remember the name Vytorin.

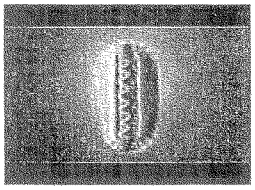


27. That's Vytorin.

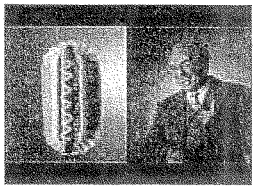
DDB

20550017(1)

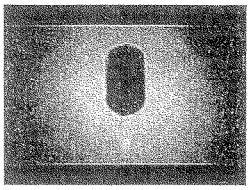
VYTORIN "Grandpa Frank" Percents :60



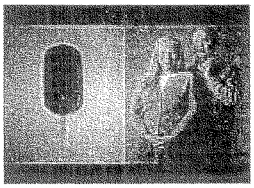
1. Cholesterol comes from 2 sources. It's not only from that foot-long frank,



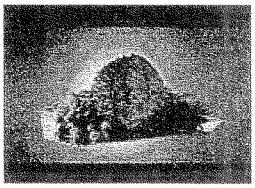
2. but from your Grandpa Frank.



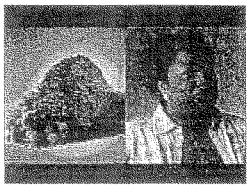
3. Not just from that ice-cream pop,



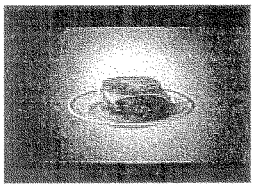
4. but from mom and pop as well.



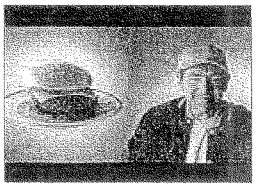
5. And not just from that Virginia ham,



6. but from your Aunt Ginnie too.



7. Your cholesterol doesn't just come from food.



8. It also has a lot to do with family history.



9. Ask your doctor about Vytorin.

SUPER: Available by prescription only

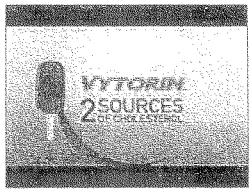


10. A healthy diet is important, but when it's not enough, adding Vytorin can help.

SUPER: Available by prescription only



11. Vytorin treats the two sources of cholesterol--



12. food

MSPP 165548.11

DDB

20550017(1)

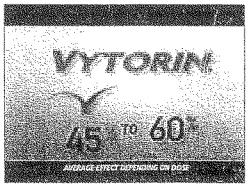
VYTORIN "Grandpa Frank" Percents :60



13. and what your body makes naturally based on family history.

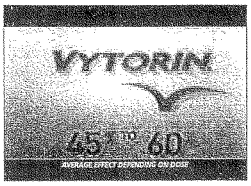


14. Vytorin lowers bad cholesterol



15. 45% to

SUPER: Average effect depending on dose



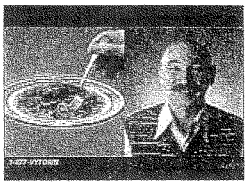
16. 60%.

SUPER: Average effect depending on dose



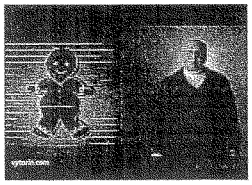
17. Vytorin is not for everyone, including people with liver problems, women who are nursing, pregnant, or may become pregnant.

SUPER: See our ad in Cooking Light



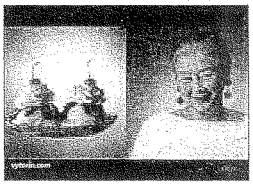
18. Unexplained muscle pain or weakness could be a sign of a rare but serious side effect.

SUPER: 1-877-VYTORIN



19. Vytorin may interact with other medicines or certain foods, increasing your risk of getting this serious side effect.

SUPER: vytorin.com



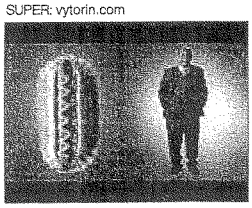
20. Simple blood tests are needed to check for liver problems.

SUPER: vytorin.com



21. Follow a healthy diet and ask your doctor about adding Vytorin.

SUPER: Ask your doctor



22. For the two sources of cholesterol–



23. remember the name Vytorin.



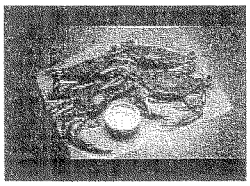
24. That's Vytorin.

MSPP 165548.12

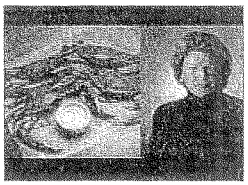
DDB

20550617(1)

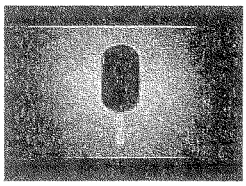
VYTORIN "Aunt Betty" Lipitor :60



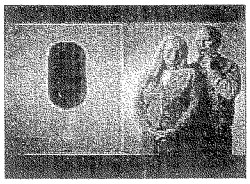
1. Cholesterol comes from 2 sources. It's not only from that buttered crab,



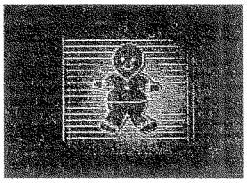
2. but from your crabby Aunt Betty.



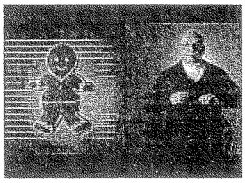
3. And not just from that ice cream pop



4. but from your mom and pop as well.



5. Your cholesterol doesn't just come from food.



6. It also has a lot to do with family history.



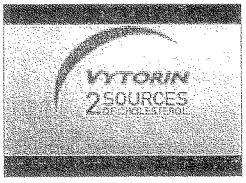
7. Ask your doctor about Vytorin.

SUPER: Available by prescription only



8. A healthy diet is important, but when it's not enough, adding Vytorin can help.

SUPER: Available by prescription only



9. Vytorin treats the two sources of cholesterol--



10. food



11. and what your body makes naturally based on family history.



12. Vytorin was proven in clinical studies to lower

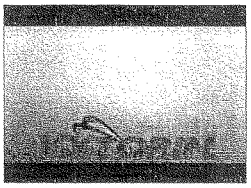
MSPP 165548.13

20550617(1)

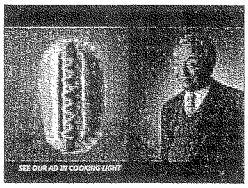
VYTORIN "Aunt Betty" Lipitor :60



13. bad cholesterol more

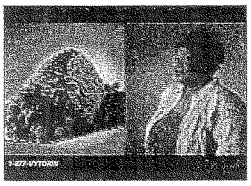


14. than Lipitor alone.



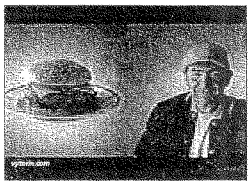
15. Vytorin is not for everyone, including people with liver problems, women who are nursing, pregnant, or may become pregnant.

SUPER: See our ad in Cooking Light



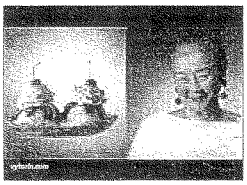
16. Unexplained muscle pain or weakness could be a sign of a rare but serious side effect.

SUPER: 1-877-VYTORIN



17. Vytorin may interact with other medicines or certain foods, increasing your risk of getting this serious side effect.

SUPER: vytorin.com



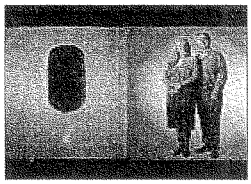
18. Simple blood tests are needed to check for liver problems.

SUPER: vytorin.com



19. Follow a healthy diet and ask your doctor about adding Vytorin.

SUPER: Ask your doctor



20. For the two sources of cholesterol–



21. remember the name Vytorin.

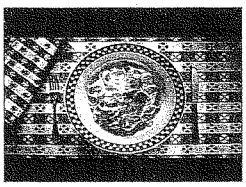


22. That's Vytorin.

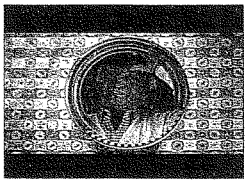
DDB

20551249(1)

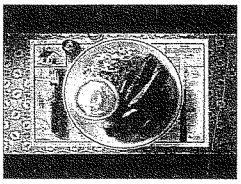
VYTORIN® "Reflections" :60



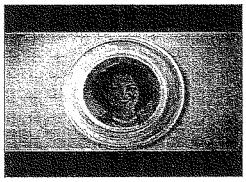
1. VO: Cholesterol. It can come from fettuccini alfredo,



2. But also from your Grandpa Alfredo.



3. From barbecue ribs,

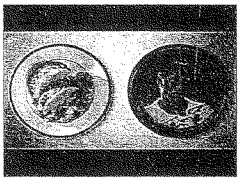


4. And from your Aunt Barbie.

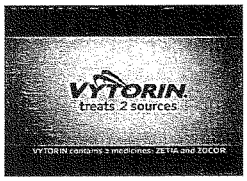


5. A healthy diet is important. When that's not enough, adding Vytorin can help.

SUPER: Available by prescription only



6. Cholesterol comes from 2 sources – food and family.



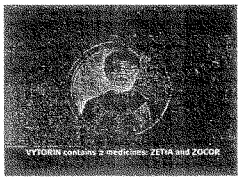
7. Vytorin treats 2 sources. Only Vytorin helps block the absorption of

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



8. cholesterol from food

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



9. and reduces the cholesterol your body makes naturally, based on family history.

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR

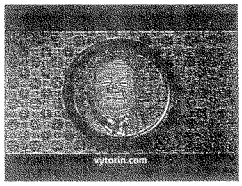


10. Vytorin was also proven in clinical studies to lower bad cholesterol more than Lipitor alone.



11. Vytorin is not for everyone, including people with liver problems, women who are nursing, pregnant, or may become pregnant.

SUPER: See our ad in *Cooking Light*



12. Unexplained muscle pain or weakness could be a sign of a rare but serious side effect.

SUPER: vytorin.com

MSPP 165548.15

DDB

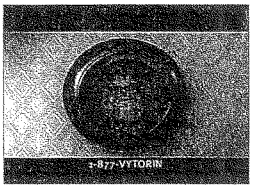
20551249(1)

VYTORIN® "Reflections" :60



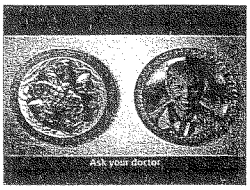
13. Vytorin may interact with other medicines or certain foods, increasing your risk of getting this serious side effect.

SUPER: 1-877-VYTORIN



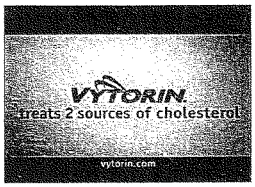
14. Simple blood tests are needed to check for liver problems.

SUPER: 1-877-VYTORIN



15. So eat right, stay active, but if that's not enough? Ask your doctor about adding Vytorin.

SUPER: Ask your doctor



16. 2 sources of cholesterol. Treat 'em both, with Vytorin.

SUPER: vytorin.com

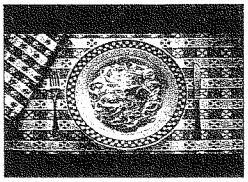
Merck_vytorin_2006_1_09_vytorin_Vytorin_1_18_reflections.indd

MSPP 165548.16

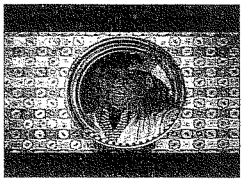
DDB

20551249(2)

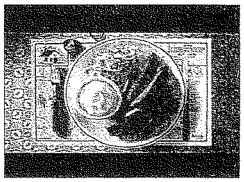
VYTORIN® "Reflections Revised" :60



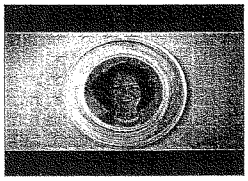
1. VO: Cholesterol. It can come from fettuccini alfredo,



2. But also from your Grandpa Alfredo.



3. From barbecue ribs,

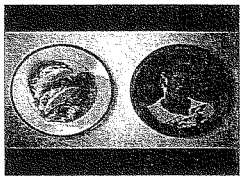


4. And from your Grandma Barbie.



5. A healthy diet is important. When that's not enough, adding Vytorin can help.

SUPER: Available by prescription only

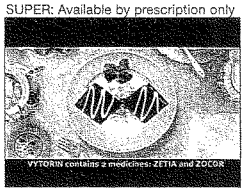


6. Cholesterol comes from 2 sources – food and family.



7. Vytorin treats 2 sources. Only Vytorin helps block the absorption of

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



8. cholesterol from food

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



9. and reduces the cholesterol your body makes naturally, based on family history.

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR

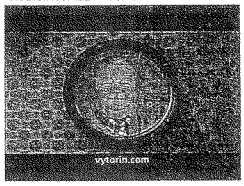


10. Vytorin was also proven in clinical studies to lower bad cholesterol more than Lipitor alone.



11. Vytorin is not for everyone, including people with liver problems, women who are nursing, pregnant, or may become pregnant.

SUPER: See our ad in *Cooking Light*



12. Unexplained muscle pain or weakness could be a sign of a rare but serious side effect.

SUPER: vytorin.com

MSPP 165548.17

DDB

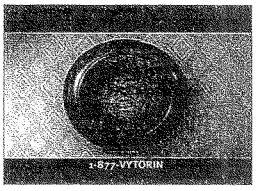
20551249(2)

VYTORIN® "Reflections Revised" :60



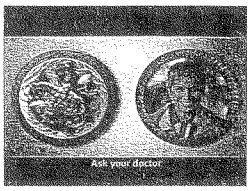
13. Vytorin may interact with other medicines or certain foods, increasing your risk of getting this serious side effect.

SUPER: 1-877-VYTORIN



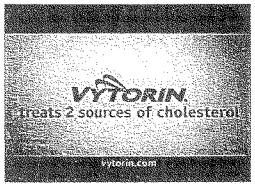
14. Simple blood tests are needed to check for liver problems.

SUPER: 1-877-VYTORIN



15. So eat right, stay active, but if that's not enough? Ask your doctor about adding Vytorin.

SUPER: Ask your doctor



16. 2 sources of cholesterol. Treat 'em both, with Vytorin.

SUPER: vytorin.com

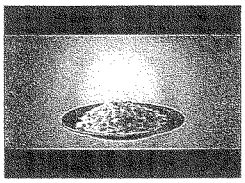
Merck_vytorin_2006_1_06_vytorin_Vytorin_p2_1_18b_reflections.indd

MSPP 165548.18

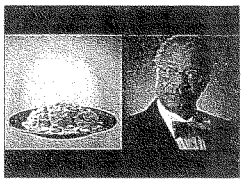
DDB

20551381(1)

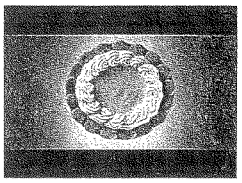
VYTORIN® "Grandfather Bo" :60



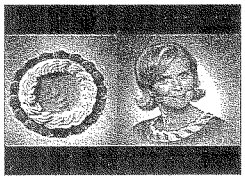
1. VO: Cholesterol. It can come from bowtie pasta,



2. but also from your Grandfather Bo.



3. From that pie, creamy banana,

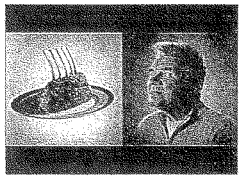


4. and your mom, Juliana.



5. A healthy diet is important. When that's not enough, adding Vytorin can help.

SUPER: Available by prescription only

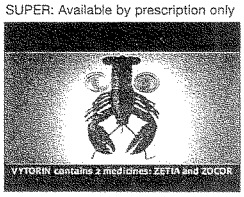


6. Cholesterol comes from 2 sources – food and family.



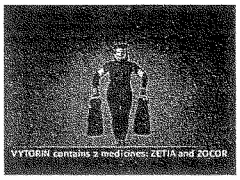
7. Vytorin treats 2 sources. Only Vytorin helps block the absorption of

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



8. cholesterol from food

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



9. and reduces the cholesterol your body makes naturally.

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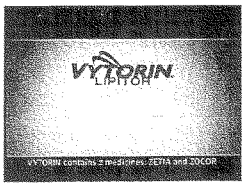

10. Vytorin was also proven in clinical studies to lower bad cholesterol more than Lipitor alone,

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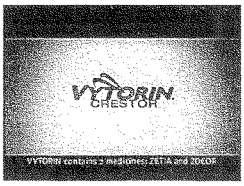
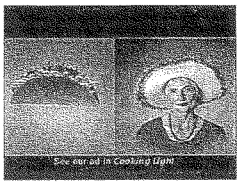


11. more than Crestor alone.

PI, p8, Table 5

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



12. Vytorin is not for everyone, including people with liver problems, women who are nursing, pregnant, or may become pregnant.

SUPER: See our ad in *Cooking Light*

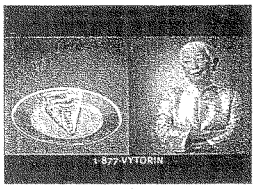
MSPP 165548.19

Clients Merck Vytorin Jobs 18442_p1 Grandpa8b_rev

DDB

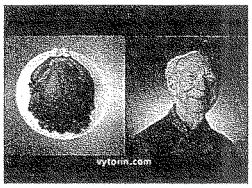
20551381(1)

VYTORIN® "Grandfather Bo" :60



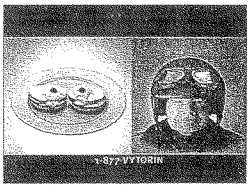
13. Tell your doctor right away about unexplained muscle pain or weakness which may be a sign of a rare but serious side effect.

SUPER: 1-877-VYTORIN



14. Certain medicines or foods may increase your risk of getting this serious side effect.

SUPER: vytorin.com



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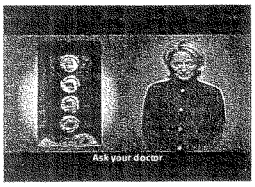
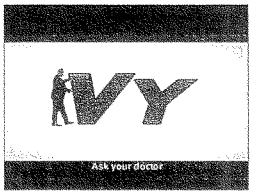
SUPER: 1-877-VYTORIN



16. So eat right, stay active,...

SUPER: Ask your doctor



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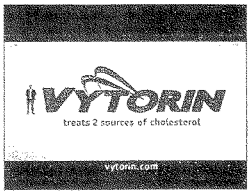


18. 2 sources of cholesterol. Treat 'em both, with Vytorin.

SUPER: vytorin.com

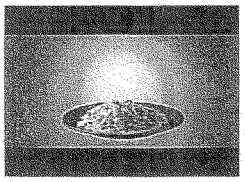
Clients Merck Vytorin Jobs 18442_p1_GrandpaBo_rev

MSPP 165548.20

DDB

20551381(2)

VYTORIN® "Grandfather Bo" REV :60



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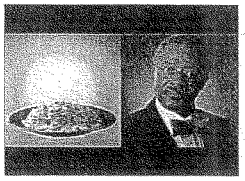
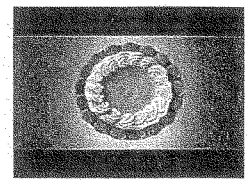


2. but also from your Grandfather Bo.



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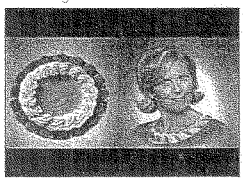

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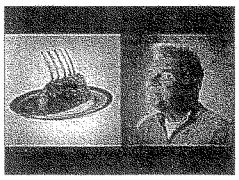
SUPER: Available by prescription only



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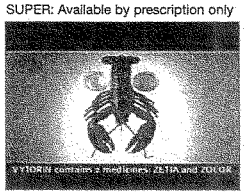
SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



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SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



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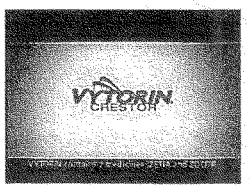

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PI, p8, Table 5

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



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SUPER: See our ad in *Cooking Light*

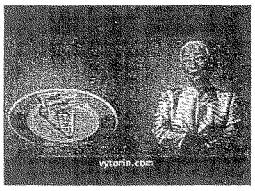
MSPP 165548.21

Clients Merck Vytorin Jobs 18442_p1_GrandpaBo_rev

DDB

20551381(2)

VYTORIN® "Grandfather Bo" REV :60



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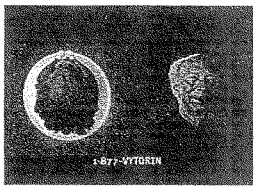
SUPER: vytorin.com



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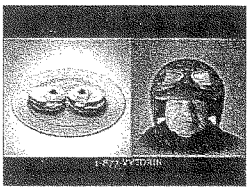
SUPER: 1-877-VYTORIN



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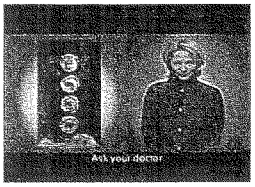

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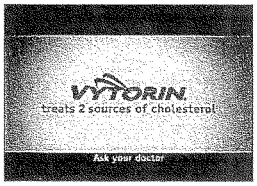

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SUPER: Ask your doctor



18. 2 sources of cholesterol. Treat 'em both, with Vytorin.

SUPER: vytorin.com

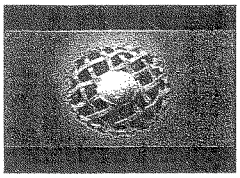
Clients Merck Vytorin Jobs 18442_p1_Grandpabo.rev

MSPP 165548.22

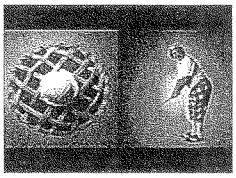
DDB

20750755(1)

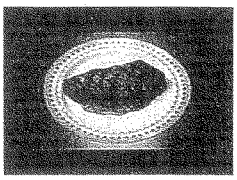
VYTORIN® "Granddad Sy" REV :60



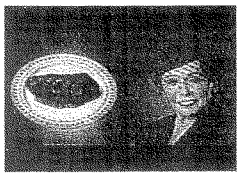
1. VO: Cholesterol. It can come from that cherry pie,



2. But also from your Granddad Sy.



3. From beef off the grill,

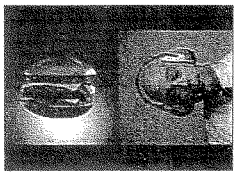


4. And your Grandmother Jill.



5. A healthy diet is important. When that's not enough, adding Vytorin can help.

SUPER: Available by prescription only



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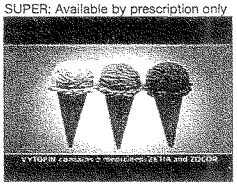
7. Vytorin treats 2 sources.

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



8. Only Vytorin helps block the absorption of cholesterol from food

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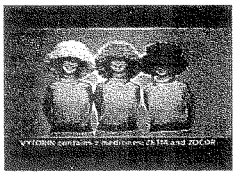

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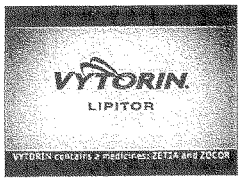

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11. more than Crestor alone.

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



12. Vytorin is not for everyone, including people with liver problems, women who are nursing, pregnant, or may become pregnant.

SUPER: See our ad in *Cooking Light*

MSPP 165548.23

DDB

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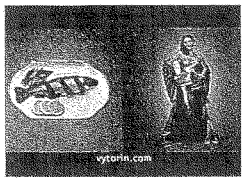
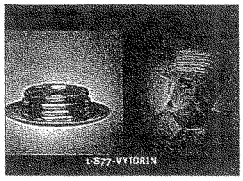
VYTORIN® "Granddad Sy" REV :60



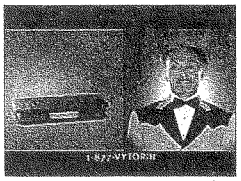
13. Tell your doctor right away about unexplained muscle pain or weakness which may be a sign of a rare but serious side effect.

SUPER: vytorin.com



14. Certain medicines or foods may increase your risk of getting this serious side effect.

SUPER: 1-877-VYTORIN



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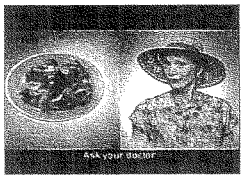

16. So eat right, stay active, but if that's not enough?

SUPER: Ask your doctor



17. Ask your doctor about adding Vytorin. 2 sources of cholesterol. Treat 'em both, with Vytorin.

SUPER: vytorin.com

MSPP 165548.24

studios3/clients/merck/jobs/vytorin/183081/8308_p4_REV_GranddadSy

DDB

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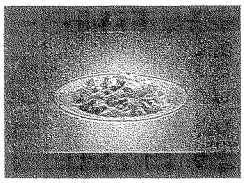
VYTORIN® "Louise" :60



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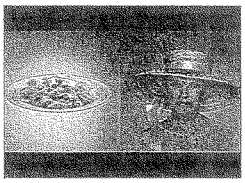

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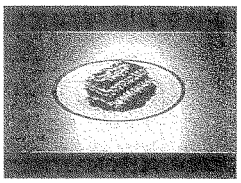
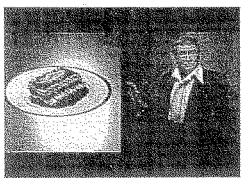


3. From Mom's lasagne, extra cheesy,

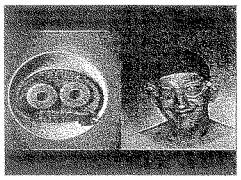


4. And your Pop, Petey.



5. A healthy diet is important. When that's not enough, adding Vytorin can help.

SUPER: Available by prescription only



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7. Vytorin treats 2 sources.

SUPER: VYTORIN contains two medicines: ZETIA and ZOCOR



8. Only Vytorin helps block the absorption of cholesterol from food

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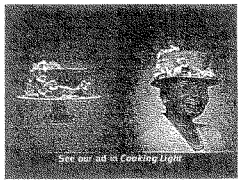

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SUPER: See our ad in *Cooking Light*

studio8 /clients/merck/vytorin/jobs/19667_p2_Vytorin_Louise

DDB

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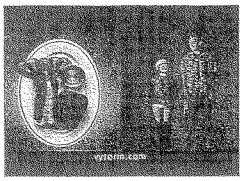
VYTORIN® "Louise" :60



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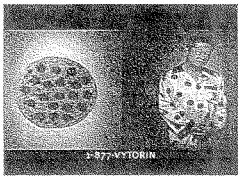
SUPER: vytorin.com



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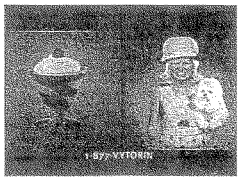
SUPER: 1-877-VYTORIN



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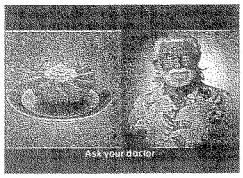

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17. Ask your doctor about adding Vytorin. 2 sources of cholesterol. Treat 'em both, with Vytorin.

SUPER: vytorin.com

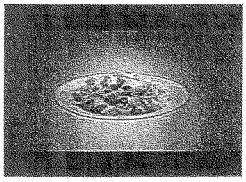
studio8 /clients/merck/vytorin/jobs/19667_q2_Vytorin_Louise

MSPP 165548.26

DDB

20752205(3)

VYTORIN® "Louise w/ chalkboard" :60



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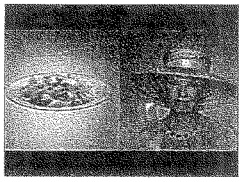

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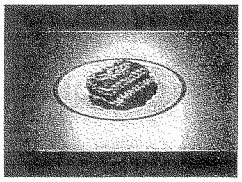

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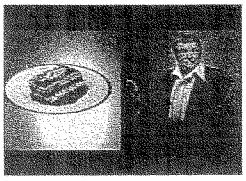

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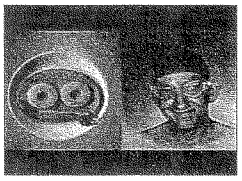

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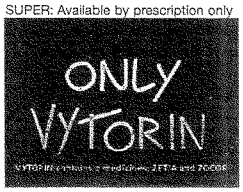

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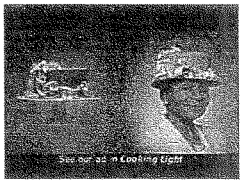

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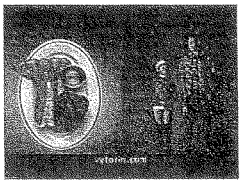
SUPER: See our ad in *Cooking Light*



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SUPER: vytorin.com

studio8:/clients/merck/vytorin/jobs/19667_p3_Vytorin_LouiseMS

DDB

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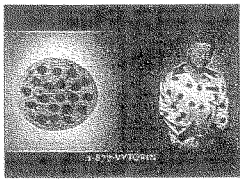
VYTORIN® "Louise w/ chalkboard" :60



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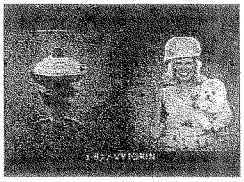
SUPER: 1-877-VYTORIN



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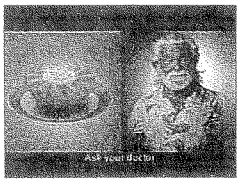

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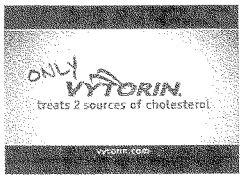

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SUPER: vytorin.com

studio8 /clients/merch/vytorin/jobs/19667_p3_Vytorin_LouiseWS

VYTORIN™
(ezetimibe/simvastatin)

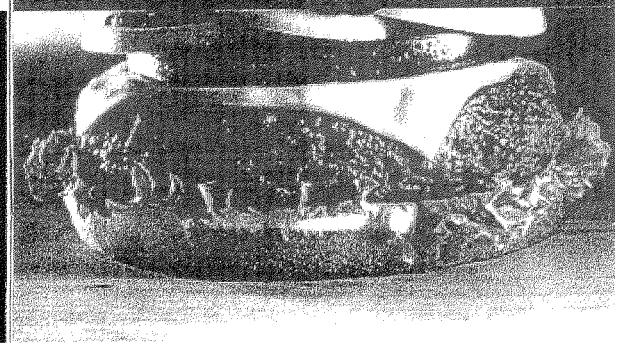
PPI, p1/A

Important information:

VYTORIN is a prescription tablet and isn't right for everyone, including women who are nursing or pregnant or who may become pregnant, anyone with liver problems, and people who are allergic to any ingredients in VYTORIN.



PPI, p1/B **VYTORIN treats both.**



VYTORIN™
(ezetimibe/simvastatin)

Bad cholesterol.

It comes from pizza...and your parents.

Nabel, pp61-62/B

You've heard it, maybe even said it: cholesterol comes from food. What you may not have heard is that cholesterol actually has more to do with your family, based on heredity.

Turley, p2/A

That may explain why your LDL (bad) cholesterol level could still be high, even though you're trying hard to lower it with diet and exercise.

You see, in addition to the cholesterol that comes from foods you eat, cholesterol is also produced in your body. It's something you get from your mom, your dad, even your grandparents.

Nabel, pp61-62/B

So, if you're having a hard time lowering your cholesterol, in spite of dieting and exercising, don't blame yourself. Everyone's bad cholesterol comes from **2** sources. And targeting both is an effective way to lower it.

Shepherd, p3/A,B

The good news is that you can target both sources with a product that helps block absorption of cholesterol from food *and* reduces the cholesterol that your body makes.

PPI, p1/B

2 sources of bad cholesterol.

The first is food, the second is your body.

With 2 sources of cholesterol to deal with, it's no wonder that so many adults have high cholesterol. Most folks aren't even sure where cholesterol comes from.

American Heart, p1/B

Cholesterol from the foods you eat.

Cholesterol from food is hard to get away from, even though you may be watching your diet. All foods of animal origin contain cholesterol, including eggs, red meat, and shrimp. Although foods that are high in saturated fats or trans fats should also be avoided. These include foods you may not even think of, such as:

- Grilled-cheese sandwich
- Margarine
- Potato with butter
- Chicken pot pie

WebMD, p1/A,B,C

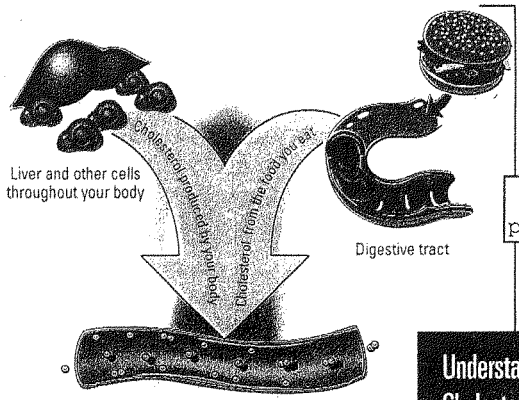
As you eat, cholesterol from food is absorbed by your digestive tract. It then makes its way into your liver and can circulate through your body in your bloodstream. That's one source. There's also a little-known second source of cholesterol—your body.

Nabel, p61/A

Cholesterol produced by your body, based on heredity.

Like many people, you may not know that your body produces cholesterol naturally, based on heredity—despite the fact that it's where more of

Nabel, pp61-62/B



Nabel, p61/A, pp61-62/B

Understanding Cholesterol

Turley, p2/A

your total cholesterol comes from. Your liver makes cholesterol, as do other individual cells throughout your body. Once cholesterol is produced, it can make its way into your bloodstream.

Nabel, p61/A

What does this process mean to you? Take the cholesterol your body makes and add it to the cholesterol you get from food. Now you can see how easily cholesterol can build up in your bloodstream and how your overall cholesterol level can increase.

About Your Cholesterol, p2/B

The good news is, treating both sources can significantly lower your cholesterol.

Shepherd, p3/A

VYTORIN™ (ezetimibe/simvastatin)

The only product that:

- Helps block the absorption of cholesterol that comes from food
- Reduces the cholesterol your body makes naturally

The result is that less bad cholesterol ends up in your bloodstream. *And that's good for your health.*

American Heart, p3/E

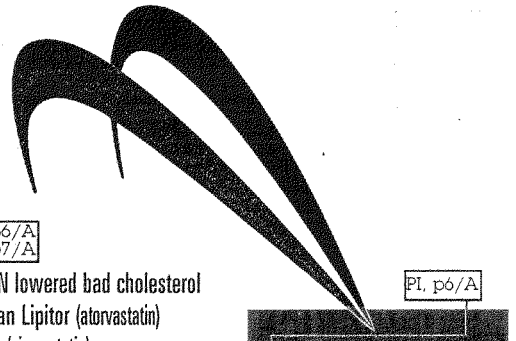
VYTORIN can:

- Lower LDL (bad) cholesterol
- Lower total cholesterol
- Lower triglycerides (fatty substances in your blood)
- Raise HDL (good) cholesterol

Just 1 pill a day.

Your doctor may decide that, along with diet and exercise, VYTORIN is right for you. If so, remember to take 1 pill a day in the evening, as your doctor prescribes. Take VYTORIN with or without food—the choice is yours.

PPI, p2/A



PI, p6/A
p7/A

VYTORIN lowered bad cholesterol more than Lipitor (atorvastatin) or Zocor (simvastatin).

In clinical studies involving people with high cholesterol, VYTORIN was proven to lower bad cholesterol more than Lipitor and Zocor.

PI, p6/A

VYTORIN is proven to lower bad cholesterol 52% to 60%

Important information:

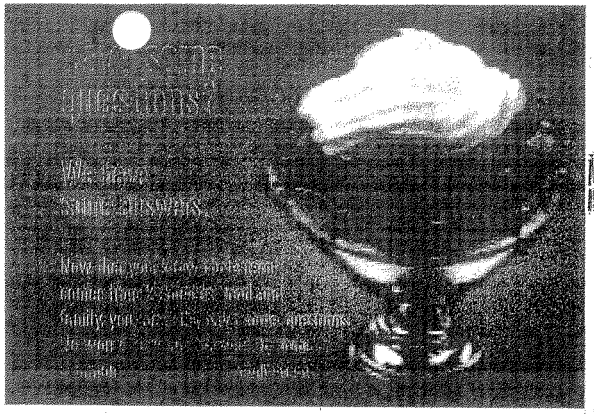
Unexplained muscle pain or weakness could be a sign of a rare but serious side effect and should be reported to your doctor right away.

PPI, p1/D

Your doctor may do simple blood tests before and during treatment with VYTORIN to check for liver problems. To help avoid serious side effects, discuss with your doctor medicine or food you should avoid while on VYTORIN.

PPI, p2/B

VYTORIN™
(ezetimibe/simvastatin)



Q. What is cholesterol?

American Heart, p1/A

A. Cholesterol is a soft, waxy substance found in your bloodstream. Although your body needs cholesterol to help build and maintain cells, too much cholesterol can build up on your artery walls.

Q. What are LDL cholesterol and HDL cholesterol?

A. LDL (low-density lipoprotein) cholesterol is known as "bad cholesterol" because it can build up in the walls of your arteries and form a thick, hard plaque that clogs your arteries and blocks the flow of blood to your heart and brain. HDL refers to high-density lipoprotein cholesterol, also called "good cholesterol" because it helps eliminate bad cholesterol from the body.

American Heart, p2/C,D

American Heart, p10/G

Q. What can happen if I do have high cholesterol?

A. Having high LDL (bad) cholesterol can put you at risk for heart disease, heart attack, or stroke—especially if you have any of these additional risk factors:

- ❑ Low HDL cholesterol
- ❑ Diabetes
- ❑ Smoking
- ❑ Obesity
- ❑ High blood pressure
- ❑ Lack of physical activity
- ❑ Family history of heart disease
- ❑ High-fat/high-cholesterol diet
- ❑ Men aged 45 or older
- ❑ Women aged 55 or older



VYTORIN
(ezetimibe/simvastatin)

Q. What should I do?

American Heart, p10/G

A. The first thing to do is have your cholesterol checked and to talk to your doctor to find out your LDL (bad) cholesterol goal. (Use the *Goal Card* in the back pocket of this brochure to help you keep track.) Watching your diet and exercising can help, but if your cholesterol still is not low enough, your doctor may suggest adding a medication to your routine.



VYTORIN™
(ezetimibe/simvastatin)



Q. Can VYTORIN™ (ezetimibe/simvastatin) help me lower my bad cholesterol?

A. Yes. VYTORIN is proven to lower bad cholesterol 52% to 60% (average effect based on dose) when diet and exercise aren't enough. It's the only product to help block the absorption of cholesterol and reduce the cholesterol your body makes naturally. You should still exercise and watch your diet while taking VYTORIN.

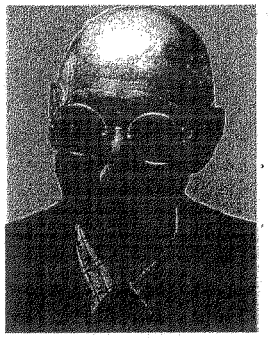
PI, p6/A

PPI, p1/B

Important information:

PPI, p2/C

In clinical studies, side effects included headache and muscle pain.



NHLBI-NCEP, p5/A,B

A healthy diet — good tasting and good for you.

Eating healthy is a vital part of lowering your cholesterol. To help make it easier, start small by making a few substitutions in your diet. Replace steaks, burgers, and fried foods with fish, chicken, and turkey that's baked or broiled. The American Heart Association has delicious recipes that can show you how to eat healthy without giving up everything that tastes good. You can find them at www.deliciousdecisions.org.

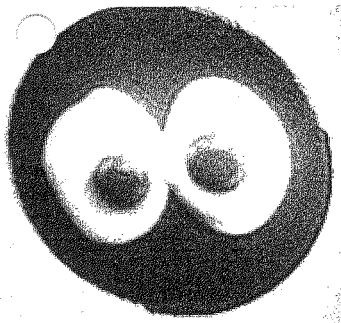
Exercise — a little goes a long way.

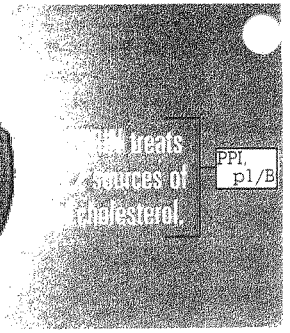
NHLBI-NCEP, p5/C

Getting regular exercise doesn't necessarily mean putting yourself through something that seems like boot camp. Little things can help you more than you think. Simply going for walks or taking stairs instead of an elevator can make a difference and help lower your cholesterol.

If you're feeling more ambitious, join a gym or explore new sports like golf, softball, or tennis. Do things you like to do, and have fun with it. The best way to make sure you stick to an exercise program is to make sure you're enjoying yourself. Better yet, get a friend to join you. Of course, you should be sure to talk to your doctor before starting any exercise regimen.

American Heart, p11/H,I,J p12/K





PPI, p1/B

Medication — may help lower your cholesterol further.

With 2 sources of cholesterol to deal with, lowering LDL (bad) cholesterol can be challenging. So, when diet and exercise aren't enough, your doctor may add VYTORIN.

American Heart, p7/F

When taking any medication, be sure to follow your doctor's recommendations and continue to take your medicine as directed.

Take these next steps — for healthier living.

1. Look at our *Lifestyle Tips* in the pocket of this brochure for helpful diet and exercise tips you can use every day.
2. Take the *Questions for your Doctor* to your next appointment, and use the *Goal Card* to log your cholesterol levels after each visit.

VYTORIN®
(ezetimibe/simvastatin)



Talk with your doctor to learn if VYTORIN is right for you.

Want more information?
These resources can help.

American Heart Association
National Center
7272 Greenville Avenue
Dallas, TX 75231
1-800-AHA-USA-1 (1-800-242-8721)
www.americanheart.org

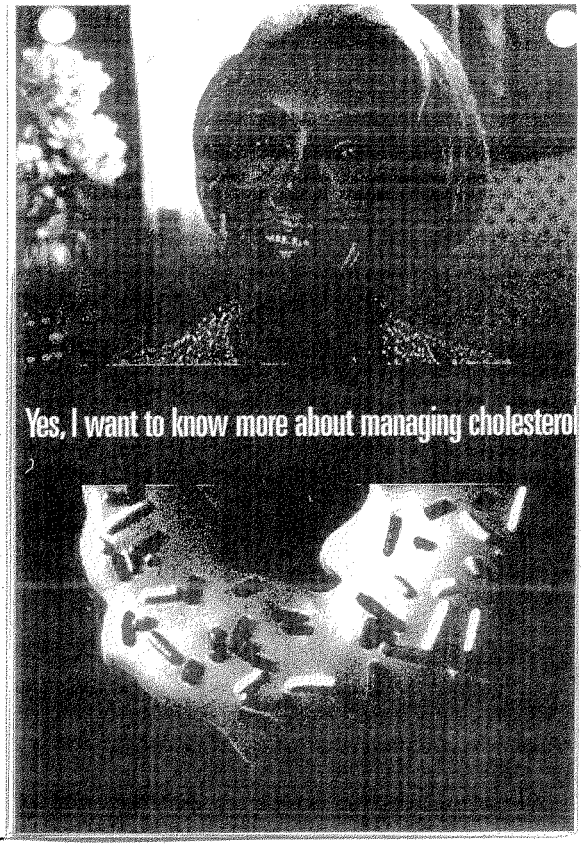
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
301-496-4000
www.nih.gov

National Cholesterol Education Program
NHLBI Information Center
PO Box 30105
Bethesda, MD 20824-0105
301-592-8573
www.nhlbi.nih.gov

For more information, visit vytorin.com

Please read the Patient Product Information enclosed in the pocket of this brochure.

VYTORIN™
(ezetimibe/simvastatin)



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Want more information?

To receive information, please check the highlighted sections on all 3 panels, sign, and mail. (We've already paid the postage for you.)

Tell us a little more about yourself.

First name

Last name

Address

City

State ZIP Birth date (Month/Day/Year)

Sex: ❑ Male ❑ Female

How would you prefer to receive further communications from us?

❑ E-mail ❑ Postal mail

E-mail address

Are you taking any of the following medications?

❑ VYTORIN™ (ezetimibe/simvastatin) ❑ Zocor (simvastatin) ❑ Crestor (rosuvastatin)
❑ Pravachol (pravastatin) ❑ Lescol (fluvastatin) ❑ Lipitor (atorvastatin)
❑ Mevacor (lovastatin) ❑ ZETIA® (ezetimibe) ❑ Other _____
❑ I'm not currently taking any cholesterol-lowering medication _____

If you're not currently taking a medication, have you ever been diagnosed with high cholesterol?

❑ Yes ❑ No

Have you ever been diagnosed with, or are you currently being treated for, any of the following?
(Check all that apply.)

❑ Diabetes ❑ High blood pressure

Do you have heart disease or a family history of heart disease?

❑ Yes ❑ No

Moisten here

Manage your cholesterol by staying informed.

Sign up to receive information about:

- ► Diet
- ► Exercise
- ► Lifestyle tips
- ► Cholesterol treatment



We've gone to great lengths to protect your privacy. Please read the Merck/Schering-Plough Privacy Commitment to you.

Please enter the following information to receive additional information about VYTORIN™ (ezetimibe/simvastatin) Tablets.

Merck/Schering-Plough's Privacy Commitment

The information you provide will be available to the Merck/Schering-Plough Pharmaceuticals family of companies (collectively, "Merck/Schering-Plough") and others working on behalf of Merck/Schering-Plough, and according to the same standards, to provide the information and services you request. Personal information about you will not otherwise be disclosed for marketing purposes without your permission. Merck/Schering-Plough reviews personal information and nonidentifiable information not only to provide the requested information and services but also to develop and offer additional services and communications that we believe our customers might find of interest. Merck/Schering-Plough also may use personal information to audit its resources for compliance and security purposes.

By providing your name, address, and other personal information, and by signing below, you agree to permit Merck/Schering-Plough, and others working on behalf of Merck/Schering-Plough, to use this information to provide information about VYTORIN that you have requested.

Check below to receive more information about VYTORIN.

Occasionally, Merck/Schering-Plough sends e-mail and other communications about new resources or services related to VYTORIN. Please check the box below this paragraph if you would like to receive additional information in the future about VYTORIN. At any time, you can request a copy of your selections on this form and that personal information about you be removed from the Merck/Schering-Plough contact list for VYTORIN by calling 1-888-851-9086.

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Please give us your permission by signing here.

Please don't forget to sign to receive the information you're requesting.

Signature*_____

Date _____

**If you are unable to sign, your spouse, legal representative, parent (if you are a minor), or other person financially responsible for you may sign on your behalf.*

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AboutYourCholesterol

The Complete Site To Controlling High Cholesterol and Maintaining Good Heart Health...

- What is Cholesterol?
- Blood Cholesterol vs. Dietary Cholesterol
- Good vs. Bad Cholesterol
- Risk Factor
- Testing and Prevention
- Cholesterol Reducing Supplement
- Check Your Cholesterol and Heart Disease IQ
- Answers to the Cholesterol and Heart Disease I.Q. Quiz
- Beta Sitosterol Shown To Reduce Cholesterol Levels in Controlled Study
- Cholesterol Risk Chart
- Low Cholesterol Diet Plan

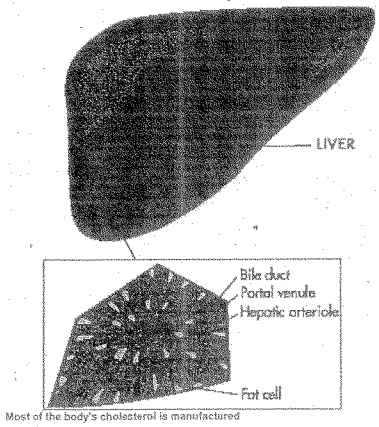
Free Copy
LOWER CHOLESTEROL WITHOUT DRUGS
by Roger Mason
A Practical Guide to Using Diet and Supplements for Healthy Cholesterol Levels

Everything you need to know about cholesterol and ways you can reduce or control high cholesterol to minimize your risk of heart attack or stroke.

Cholesterol is a waxy, fat-like compound that belongs to a class of molecules called steroids. It's found in many foods, in your bloodstream and in all your body's cells. If you had a handful of cholesterol, it might feel like a soft, melted candle. Cholesterol is essential for:

- Formation and maintenance of cell membranes (helps the cell to resist changes in temperature and protects and insulates nerve fibers)
- Formation of sex hormones **(progesterone, testosterone, estradiol, cortisol)**
- Production of bile salts, which help to digest food
- Conversion into vitamin D in the skin when exposed to sunlight.

Cholesterol is made primarily in your liver (about 1,000 milligrams a day), but it is also created by cells lining the small intestine and by individual cells in the body.



Most of the body's cholesterol is manufactured

High cholesterol is responsible for 70% of heart disease and is the leading killer of both men and women after the age of 45. It leads to arterial blockage, heart attacks, hardening of the arteries, blood clots, clogged arteries, and stroke.

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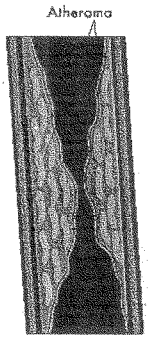

Coronary Artery
This coronary artery is becoming dangerously blocked as the cholesterol builds up.

The average American man eats about 360 milligrams of cholesterol a day; the average woman eats between 220 and 260 milligrams daily. So how are we doing? The American Heart Association recommends that we limit our average daily cholesterol intake to less than 300 milligrams. Obviously, people with high levels of cholesterol in the blood should take in even less.

Back to top

Blood Cholesterol vs. Dietary Cholesterol

It may surprise you to know that our bodies make all the cholesterol we need. When your doctor takes a blood test to measure your cholesterol level, the doctor is actually measuring the amount of circulating cholesterol in your blood, or your **blood cholesterol level**. About 85 percent of your blood cholesterol level is **endogenous**, which means it is produced by your body. The other 15 percent or so comes from an external source -- your diet. Your dietary cholesterol originates from meat, poultry, fish, seafood and dairy products. It's possible for some people to eat foods high in cholesterol and still have low blood cholesterol levels. Likewise, it's possible to eat foods low in cholesterol and have a high blood cholesterol level.

So, why is there so much talk about cholesterol in our diet? It's because the level of cholesterol already present in your blood can be increased by high consumption of cholesterol and saturated fat in your diet. This increase in dietary cholesterol has been associated with the build-up of plaques that can narrow or block blood vessels. (Think about what happens to your kitchen drain pipes when you pour chicken fat down the sink.) If the coronary arteries of the your heart become blocked, a heart attack can occur. The blocked artery can also develop rough edges. This can cause plaques to break off and travel, obstructing blood vessels elsewhere in the body. A blocked blood vessel in the brain can trigger a stroke. **High cholesterol is responsible for 70% of heart disease and is the leading killer of both men and women after the age of 45.** It leads to arterial blockage, heart attacks, hardening of the arteries, blood clots, clogged arteries, and stroke.

The average American man eats about 360 milligrams of cholesterol a day; the average woman eats between 220 and 260 milligrams daily. So how are we doing? The American Heart Association recommends that we limit our average daily cholesterol intake to less than 300 milligrams. Obviously, people with high levels of cholesterol in the blood should take in even less.

Good vs. Bad Cholesterol

Comments about "good" and "bad" cholesterol refer to the type of carrier molecule that transports the cholesterol. These carrier molecules are made of protein and are called apoproteins. They are necessary because cholesterol and other fats (lipids) can't dissolve in water, which also means they can't dissolve in blood. When these apoproteins are joined with cholesterol, they form a compound called lipoproteins. The density of these lipoproteins is determined by the amount of protein in the molecule. "Bad" cholesterol is the low-density lipoprotein (LDL), the major cholesterol carrier in the

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blood. High levels of these LDLs are associated with atherosclerosis. "Good" cholesterol is the high-density lipoprotein (HDL); a greater level of HDL--think of this as drain cleaner you pour in the sink--is thought to provide some protection against artery blockage.

A high level of LDL in the blood may mean that cell membranes in the liver have reduced the number of LDL receptors due to increased amounts of cholesterol inside the cell. After a cell has used the cholesterol for its chemical needs and doesn't need any more, it reduces its number of LDL receptors. This enables LDL levels to accumulate in the blood. When this happens, the LDLs begin to deposit cholesterol on artery walls, forming thick plaques. In contrast, the HDLs--the "good" guys--act to remove this excess cholesterol and transport it to the liver for disposal.

A third group of carrier molecules, the very low-density lipoproteins (VLDL) are converted to LDL after delivering triglycerides to the muscles and adipose (fat) tissue.
The levels of HDL, LDL and total cholesterol are all indicators for atherosclerosis and heart attack risk. People who have a total cholesterol level of 275 or greater (200 or less is desirable) are at significant risk for a heart attack, despite a favorable HDL level. In addition, people who have normal cholesterol levels but low HDL levels are also at increased risk for a heart attack. A chart showing risk levels for men and women can be seen at www.menshealthtech.com/cholesterol_care.htm

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Risk Factors

There are a number of factors that influence a person's cholesterol levels. They include diet, age, weight, gender, genetics, diseases and lifestyle.

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LOWER CHOLESTEROL WITHOUT DRUGS
A Practical Guide to Using Diet and Supplements for Healthy Cholesterol Levels by Roger Mason. It is available at Amazon and Barnes and Noble or you can get a free copy at www.menshealthtech.com/cholesterol_care.htm

Diet

There are two dietary factors associated with increases in blood cholesterol levels:

- Eating foods that are high in saturated fats, even if the fats themselves do not contain cholesterol. (These include foods containing high levels of hydrogenated vegetable oils, especially palm and coconut oils, avocados and other high-fat foods of vegetable origin.)
  Eating foods containing high levels of cholesterol. (This group includes eggs and red meat--the most maligned of the cholesterol culprits--as well as lard and shrimp. These foods can significantly raise blood cholesterol levels, especially when combined with foods that are high in saturated fat.)

It's important to note that only foods of animal origin contain cholesterol. Lack of awareness of this fact has led to some confusing labels at the grocery store. For example, some items that are high in saturated fats from plant sources bear labels claiming that they are 100 percent cholesterol free. The statement may be true, but it's generally misleading because it implies that the product is definitely beneficial to your health.

Aging

The blood levels of cholesterol tend to increase as we age--a factor doctors consider when deciding treatment options for patients with certain cholesterol levels.

Weight

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People who are overweight are more likely to have high blood cholesterol levels. They also tend to have lower HDL levels. The location of the excess weight also seems to play a role in cholesterol levels. A greater risk of increased cholesterol levels occurs when that extra weight is centered in the abdominal region, as opposed to the legs or buttocks.

Gender

Men tend to have higher LDL levels and lower HDL levels than do women, especially before age 50. After age 50, when women are in their post-menopausal years, decreasing amounts of estrogen are

thought to cause the LDL level to rise.

Genetics

Some people are genetically predisposed to having high levels of cholesterol. A variety of minor genetic defects can lead to excessive production of LDLs or a decreased capacity for their removal. This tendency towards high cholesterol levels is often passed on from parents to their children. If your parents have high cholesterol, you need to be tested to see if your cholesterol levels are also elevated.

Diseases

Diseases such as diabetes can lower HDL levels, increase triglycerides and accelerate the development of atherosclerosis. High blood pressure, or hypertension, can also hasten the development of atherosclerosis, and some medications used to treat it can increase LDL and triglycerides and decrease HDL levels.

Lifestyle

Factors that negatively affect cholesterol levels also include high levels of stress, which can raise total cholesterol levels, and cigarette smoking, which can lower a person's HDL level as much as 15 percent. On the other hand, strenuous exercise can increase HDL levels and decrease LDL levels. Exercise also can help reduce body weight, which, in turn, can help reduce cholesterol. Recent research has shown that moderate alcohol use (one drink per day for women, two drinks a day for men) can raise HDL cholesterol and therefore reduce the risk of heart attack. Despite such research, it is difficult to recommend the habitual use of alcohol because there are also negative health consequences associated with alcohol use and a high potential for abuse.

Always remember that risk factors for high cholesterol and cardiovascular disease don't exist in a vacuum--they tend to amplify each other. Reducing the risk of a cardiovascular disease involves eliminating all of the risk factors that we can control and seeking medical advise for those we can't.

Testing and Prevention

How often should I have my cholesterol levels tested?

You should get your cholesterol tested every three to five years, more often if you have high cholesterol levels. Please refer to the table below for guidelines for total cholesterol, LDL and HDL levels.

	Desirable	Borderline	Undesirable
Total Cholesterol	Below 200	200-240	Above 240
HDL Cholesterol	Above 45	35-45	Below 35
LDL Cholesterol	Below 130	130-160	Above 160
Total Cholesterol/HDL	Below 4.5	4.5-5.5	Above 5.5
LDL/HDL	Below 3	3-5	Above 5

Figure 1 - Blood Type Relationships

A convenient at home test kit which measures total cholesterol is helpful in between formal tests. You can obtain home test kits at www.menshealthtech.com/cholesterol_care.htm

What Can You Do To Reduce Your Cholesterol?

There are several steps you can take to reduce your cholesterol levels. The first is to eat a low-fat, low-cholesterol diet. That means keeping your total fat consumption--saturated, polyunsaturated and monounsaturated--to fewer than 30 percent of your daily intake of calories Remember to keep your cholesterol intake to fewer than 300 milligrams per day. Saturated fats contained in butter, whole milk, hydrogenated oils, chocolate shortening, etc. should comprise **no more than one third of your total fat consumption. To reduce your total fat and cholesterol intake, limit your consumption** of meats such as beef, pork, liver and tongue (always trim away excess fat). In addition, avoid cheese, fried foods, nuts and cream, and try to curb your intake of eggs to no more than four per week. Try to eat meatless meals several times a week, use skim milk

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and include fish in your diet. Eat a wide variety of vegetables, pasta, grains and fruit. Another good tip is to look at the package label of the foods you buy, and restrict your choices to foods containing 3 grams of fat or less per serving. For low cholesterol diet recommendations and specific foods and food groups to avoid go to **www.menshealthtech.com/cholesterol_care.htm**

There is evidence that water-soluble fibers can aid in lowering cholesterol; these foods include the fiber in oat or corn bran, beans and legumes, pectin found in apples and other fruits, and guar that is used as a thickener. Although highly touted by the media and health food stores, the phospholipid Lecithin has not been confirmed as a reducer of blood cholesterol levels. What has been found to be effective is supplements containing **Beta–sitosterol** an natural substance from plant souces. **Guggul lipids** have long been known to reduce total cholesterol and recent studies have established their effectiveness over a 6-9 month period.

If you are overweight, trying to lose weight and including aerobic exercise in your routine can help raise those desirable HDL levels. Diet and exercise alone can decrease cholesterol levels by up to 15 percent.

It probably comes as no surprise to you that, if you smoke, you should quit to avoid a wide range of health problems, including lower HDL levels and increased risk of heart disease and heart attack.

Back to top

Cholesterol Reducing Supplements

It is entirely possible to use natural herbs and nutritional supplements to assist in lowering overall cholesterol, raise HDL while lowering LDL and triglycerides. Numerous studies support the value of supplements, which support healthy cholesterol levels with very few cases of side effects often experienced with drugs. When supplements are taken in combination of a low cholesterol diet and moderate exercise, remarkable results have often been experienced.

Are Cholesterol Reducing Supplements Right For You?

We highly recommend
LOWER CHOLESTEROL WITHOUT DRUGS
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While supplements are not a substitute for proper medical treatment many mainstream practitioners are recommending natural alternatives in cases where patients are not in high-risk categories. Is cholesterol reducing supplementation right for you? That certainly depends on your overall health condition, medical history and current level and ratio of cholesterol. The following list of supplements known to be valuable in dealing with cholesterol problems is in part taken from research and studies in the U.S. and abroad.

A portion of this research has been compiled in a book by Roger Mason *"LOWER CHOLESTEROL WITHOUT DRUGS"* Available at Amazon, Barnes and Nobel or a free download can be obtained at **www.menshealthtech.com/cholesterol_care.htm**

Cholesterol Reducing Supplements

Beta-sitosterol. Beta-sitosterol is a healthy plant oil, found in all vegetable matter, but in minute quantities, except in sugar cane, soybeans and rice. It can decrease the absorption of cholesterol in the digestive system and decrease the amount of cholesterol produced by the liver. Beta-Sitosterol decreases absorption by locking to the fat molecules eaten and by blocking the fat molecule absorption gates in the intestines. The fats and cholesterol are then excreted rather than absorbed. A study in the American Journal of Clinical Nutrition showed a 42% decease in cholesterol absorbed when taking beta-sitosterol before eating scrambled eggs.

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At McGill University in Montreal (Can. J. Physiol. Pharmacol. 75, 1997, p. 217-27) doctors did a review of the literature on beta-sitosterol and cholesterol metabolism. They researched in detail 18 major studies that used Beta sitosterol to lower cholesterol and triglycerides. They concluded," **the addition to diet of phytosterols (Beta –sitosterol) represents an effective means of improving circulating lipid profiles to reduce risk of coronary heart disease."** This study came complete with forty high quality references and left no doubt about the effectiveness of Beta sitosterol on humans.

According to Roger Mason "If there was only one supplement you could take to normalize your cholesterol it should be beta-sitosterol taken in approximately 300 mg doses every day. If you have a more serious problem you can take two capsules a day or 600 mg. Beta-sitosterol is the most studied, most proven, most effective single way I've found to lower total and LDL cholesterol".

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Guggul Lipids. Guggul is an Indian herb from the Commiphora tree that has been well known in India for centuries. This resin has been a part of Ayurvedic medicine for centuries then but has only recently been discovered in the West. It has been studied in Eastern clinics and hospitals for over 20 years. These studies have found that guggul reduces platelet stickiness so over clotting does not occur in the blood Over clotting causes strokes and heart attacks. A study in 1988 (Planta Medica volume 4, pages 271-showed guggul lipids stimulated thyroid metabolism and function. Increasing metabolism by stimulating the thyroid gland can provide weight loss without eating less.

In two Indian Journal of Medicine studies and the Journal of the Association of Physicians it was also found that the triglyceride levels were reduced significantly as well. So, in many subjects total cholesterol was lowered, HDL cholesterol raised, LDL cholesterol lowered, triglyceride levels lowered and even uric acid levels lowered.

In human clinical trials of guggul lipid, cholesterol dropped 14-27% while triglyceride levels dropped from 22-30% in a 4 to 12 week period. Studies have shown that the effect of guggul lipid on serum cholesterol and triglycerides is superior to the lipid-lowering drugs.

Chromium. Chromium is a very important trace element to take and works with the other minerals. Chromium is often deficient in our refined diets and you only need 200 mcg (a microgram is a millionth of a gram) a day. Some good multivitamins contain this but few supply the 200 mcg. required to be effective There are many studies showing the value of chromium supplementation for our health in general. The label should state "chromium (as chromium picolinate)"

Flax Seed Oil. Omega-3's not only lower cholesterol and triglyceride levels but also improves blood parameters. It is very difficult to get a good supply of omega-3 fats in your diet unless you eat a lot of fatty fish like sardines, salmon, herring and mackerel.
One of the best sources of Omega-3'is flax seed. This is a cleaner, less expensive plant product that is preferable to fish oils. Flax oil can be obtained in soft gel supplements or in liquid form at most stores.

Beta glucan is a polysaccharide found in oats, barley, yeast and mushrooms. The miraculous powers of beta glucan to lower cholesterol and triglycerides and strengthen our immune systems have been known about for more than a decade now.

Until recently it has been all but impossible to economically extract it from even inexpensive oats and leftover beer brewing yeast. Finally, in the year 2000 technology had advanced and you could get inexpensive beta glucan in 100 and 200 mg capsules very inexpensively.

We highly recommend

LOWER CHOLESTEROL WITHOUT DRUGS

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Roger Mason's book provides numerous studies, which demonstrate that beta glucan is a safe, effective, powerful, proven, and inexpensive way to lower your cholesterol levels, yet most people have never even heard of it. Most vitamin companies don't even sell it and it can be difficult to find a reliable, strong, inexpensive brand in your drug store or even in your health food store. Learn more at **www.menshealthtech.com/cholesterol_care.htm**

Soy Isoflavones There are two main isoflavones we are concerned about which are genestein and daidzein. The American Heart Nutrition Committee (Circulation, December 2000) advised Americans with high cholesterol to add soy protein to their diets. In that report Dr. Erdman said that numerous studies show that soy isoflavones lower LDL, raise HDL, lower triglycerides and lower total cholesterol levels. Endorsements from such prestigious groups as this should be heeded.

Soy isoflavones improve blood profiles significantly, improve the quality of arteries and are even shown to lower blood pressure. All of these effects have been obtained without any change in diet or exercise.

Red Yeast Rice Extract. Research has shown that red yeast rice extract significantly reduces total cholesterol, LDL cholesterol and triglycerides and increases HDL cholesterol Chinese red yeast rice extract contains
cholesterol-lowering compounds known as statins, among them lovastatin, the same active ingredient in some prescription drugs.™. Statins work by inhibiting the key enzyme (HMG-CoA reductase) responsible for producing cholesterol in the body. The results of trials using red yeast rice extract found that patients receiving red yeast rice extract experienced a total cholesterol drop of 23%, while (bad) LDL-cholesterol dropped 28.5%,
triglycerides dropped 36.5% and (good) HDL cholesterol increased 19.6%.

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Supplements Made Easy

Taking all these different supplements can be cumbersome and costly. We know of one company, which has developed a cholesterol-reducing supplement, which contains many, (but not all) of the proven natural ingredients mentioned above. Add an omega 3 supplement or liquid to their easy to use product and you will have a cost effective method of using natural supplements to support your cholesterol goals. To learn more go to **www.menshealthtech.com/cholesterol_care.htm**

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Check Your Cholesterol and Heart Disease IQ

Are you cholesterol smart? Test your knowledge about high blood cholesterol with the following statements. Click on true or false. The answers are at the bottom of this sheet.

1.	High blood cholesterol is one of the risk factors for heart disease that you can do something about?	T	F
2.	To lower your blood cholesterol level you must stop eating meat altogether?	T	F
3.	Any blood cholesterol level below 240 mg/dL is desirable for adults?	T	F
4.	Fish oil supplements are recommended to lower blood cholesterol?	T	F
5.	To lower your blood cholesterol level you should eat less saturated fat, total fat, and cholesterol, and lose weight if you are overweight?	T	F
6.	Saturated fats raise your blood cholesterol level more than anything else in your diet?	T	F
7.	All vegetable oils help lower blood cholesterol levels?	T	F
8.	Lowering blood cholesterol levels can help people who have already had a heart attack?	T	F
9.	Some natural supplements may help lower cholesterol?	T	F
10.	Women don't need to worry about high blood cholesterol and heart disease?	T	F
11.	Reading food labels can help you eat the heart healthy way?	T	F

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Answers to the Cholesterol and Heart Disease I.Q. Quiz

1.	**True**	High blood cholesterol is one of the risk factors for heart disease that a person can do something about. High blood pressure, cigarette smoking, diabetes, overweight, and physical inactivity are the others.
2.	**False**	Although some red meat is high in saturated fat and cholesterol, which can raise your blood cholesterol, you do not need to stop eating it or any other single food. Red meat is an important source of protein, iron, and other vitamins and minerals. You should, however, cut back on the amount of saturated fat and cholesterol that you eat. One way to do this is by choosing lean cuts of meat with the fat trimmed. Another way is to watch your portion sizes and eat no more than 6 ounces of meat a day. Six ounces is about the size of two decks of playing cards.
3.	**False**	A total blood cholesterol level of under 200 mg/dL is desirable and usually puts you at a lower risk for heart disease. A blood cholesterol level of 240 mg/dL is high and increases your risk of heart disease. If your cholesterol level is high, your doctor will want to check your level of LDL-cholesterol ("bad" cholesterol). A HIGH level of LDL-cholesterol increases your risk of heart disease, as does a LOW level of HDL-cholesterol ("good" cholesterol). An HDL-cholesterol level below 40 mg/dL is considered a risk factor for heart disease. A total

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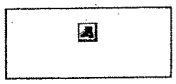

We highly recommend
LOWER CHOLESTEROL WITHOUT DRUGS
A Practical Guide to Using Diet and Supplements for Healthy Cholesterol Levels by Roger Mason. It is available at Amazon and Barnes and Noble or you can get a free copy at www.menshealthtech.com/cholesterol_care.htm

		cholesterol level of 200-239 mg/dL is considered borderline-high and usually increases your risk for heart disease. All adults 20 years of age or older should have their blood cholesterol level checked at least once every 5 years.
4.	**True**	Fish oils are a source of omega-3 fatty acids, which are a type of polyunsaturated fat. Most omega-3 supplements help to reduce blood cholesterol levels. Cold-water fish is a good food choice because it is low in saturated fat. And high in omega-3s
5.	**True**	Eating less fat, especially saturated fat, and cholesterol can lower your blood cholesterol level. Generally your blood cholesterol level should begin to drop a few weeks after you start on a cholesterol-lowering diet. How much your level drops depends on the amounts of saturated fat and cholesterol you used to eat, how high your blood cholesterol is, how much weight you lose if you are overweight, and how your body responds to the changes you make. Over time, you may reduce your blood cholesterol level by 10-50 mg/dL or even more.
6.	**True**	Saturated fats raise your blood cholesterol level more than anything else. So, the best way to reduce your cholesterol level is to cut back on the amount of saturated fats that you eat. These fats are found in largest amounts in animal products such as butter, cheese, whole milk, ice cream, cream, and fatty meats. They are also found in some vegetable oils--coconut, palm, and palm kernel oils.
7.	**False**	Most vegetable oils--canola, corn, olive, safflower, soybean, and sunflower oils--contain mostly monounsaturated and polyunsaturated fats, which help lower blood cholesterol when used in place of saturated fats. However, a few vegetable oils-- coconut, palm, and palm kernel oils--contain more saturated fat than unsaturated fat. A special kind of fat, called "trans fat," is formed when vegetable oil is hardened to become margarine or shortening, through a process called "hydrogenation." The harder the margarine or shortening, the more likely it is to contain more trans fat. Choose margarine containing liquid vegetable oil as the first ingredient. Just be sure to limit the total amount of any fats or oils, since even those that are unsaturated are rich sources of calories.
8.	**True**	People who have had one heart attack are at much higher risk for a second attack. Reducing blood cholesterol levels can greatly slow down (and, in some people, even reverse) the buildup of cholesterol and fat in the wall of the coronary arteries and significantly reduce the chances of a second heart attack. If you have had a heart attack or have coronary heart disease, your LDL level should be around 100 mg/dL which is even lower than the recommended level of less than 130 mg/dL for the general population.
9.	**True**	There are significant amounts of research supporting the use of natural supplements to assist in reducing or controlling high cholesterol levels. While not for everyone many people can benefit from adding certain supplements to their daily diet.
10.	**False**	Blood cholesterol levels in both men and women begin to go up around age 20. Women before menopause have levels that are lower than men of the same age. After menopause, a women's LDL-cholesterol level goes up--and so her risk for heart disease increases. For both men and women, heart disease is the number one cause of death.
11.	**True**	Food labels have been changed. Look on the nutrition label for the amount of saturated fat, total fat, cholesterol, and total calories in a serving of the product. Use this information to compare similar products. Also, look for the list of ingredients. The ingredient in the

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Cholesterol Care™ Is the Only Guaranteed Supplement That Contains **All Six** Natural Ingredients Proven Effective in Lowering Dangerously High Levels of Cholesterol and Triglycerides...Guaranteed to cut your cholesterol and lower your risk of heart attack or stroke while avoiding costly and often dangerous prescription drugs. Eliminate worry and health concerns.
On Sale This Week...Save 30%
No Risk Unconditional Money Back Guarantee!
Click Here To Save
www.menshealthtech.com/cholesterol_care.htm

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LOWER CHOLESTEROL WITHOUT DRUGS
A Practical Guide to Using Diet and Supplements for Healthy Cholesterol Levels by Roger Mason. It is available at Amazon and Barnes and Noble or you can get a free copy at www.menshealthtech.com/cholesterol_care.htm

greatest amount is first and the ingredient in the least amount is last. So to choose foods low in saturated fat or total fat, go easy on products that list fats or oil first, or that list many fat and oil ingredients.

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Phytosterols Shown Again to Reduce Absorption of Dietary Cholesterol

NEWSWIRE, August 20, 2003– Naturally occurring plant compounds called phytosterols are known to lower blood levels of total cholesterol and low-density lipoprotein cholesterol. As a food ingredient, they are recognized as safe by the U.S. Food and Drug Administration. The FDA has also approved a food label health claim that phytosterol esters lower the risk of coronary heart disease when used in conjunction with a low-fat diet.

RESEARCH: Researchers studied 10 volunteer subjects with normal cholesterol levels to determine the effect of naturally occurring phytosterols and phytosterol esters present in wheat germ on cholesterol absorption. All of the subjects were fed three different types of wheat-germ containing muffins as the test meals on three separate occasions. The researchers added 30 mg of cholesterol with a chemical tracer to all of the muffins so cholesterol absorption could be measured. The three treatments included 1) muffins with 80 g of wheat germ and 328 mg of naturally occurring phytosterols, 2) muffins with wheat germ in which the phytosterols had been removed and 3) muffins with wheat germ in which the removed phytosterols were added back. RESULTS: The muffins with naturally occurring phytosterols reduced cholesterol absorption by 42.8 percent, compared to the phytosterol-free wheat-germ muffins. There was no significant difference in efficiency of cholesterol absorption between the muffins with naturally occurring phytosterols and those with added purified phytosterols. IMPLICATIONS: This study demonstrated that purified plant sterols have the same cholesterol-lowering effect as naturally occurring sterols in wheat germ. Phytosterols in low-fat foods, such as wheat germ, may be useful in lowering cholesterol levels and a person's risk of heart disease. Ostlund RE, Racette SB, Stenson WF, "Inhibition of cholesterol absorption by phytosterol-replete wheat germ compared with phytosterol-depleted wheat germ." American Journal of Clinical Nutrition, 2003;77:1385- 1389.

For further information, readers are invited to download a copy of Roger Mason's **How to Lower Your Cholesterol Without Drugs.**

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What Is Cholesterol?

Cholesterol is a fatlike substance carried by the blood to every cell in the body. Some cholesterol is needed by your body to develop cell walls and help with other important body functions.

Cholesterol comes from 2 sources: your body and the foods you eat. In your body, cholesterol is made in the liver. Your liver makes all the cholesterol your body needs. Certain foods you eat provide additional amounts of cholesterol. Cholesterol in your diet comes from animal foods such as meats, whole milk, cheese, butter, and eggs.

So, while some cholesterol in your blood is essential to your health, too much can be harmful. Over time, excess cholesterol can build up on the walls of your arteries. This buildup, or plaque, narrows your arteries and reduces blood flow to the heart; this creates the risk of a heart attack.

If your level of **LDL** "bad" **cholesterol** is high (160 or greater), you are at greater risk of hardened arteries (**atherosclerosis**) and **coronary artery disease**. Making good **diet** choices is your first line of defense when striving to improve cholesterol levels. Knowing which foods to avoid and which to include will not only improve your cholesterol

levels, but will improve your overall health as well.

Exercise is also an excellent strategy for reducing levels of LDL cholesterol. If diet and exercise strategies are unsuccessful in reducing levels of LDL cholesterol, then consider **cholesterol-reducing supplements**.

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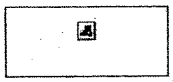

Total Cholesterol

Total cholesterol measures the combination of HDL and LDL, along with several other factors. The levels of "fats" in the blood-total cholesterol, HDL (a subset called "good cholesterol") and LDL ("bad cholesterol") and triglycerides have been used for years to predict the risk of heart disease Higher cholesterol, LDL, triglycerides, and/or low HDL all are associated with increased risk of heart diseases.

What Is "Good" Versus "Bad" Cholesterol?

Cholesterol and blood do not mix well. So, for cholesterol to travel through your blood, it is coated with a layer of protein to make lipoprotein. Two lipoproteins you may have heard about are high-density lipoprotein, or HDL cholesterol, and low-density lipoprotein, or LDL cholesterol.

"Good"- HDL Cholesterol

High-density lipoprotein, or HDL cholesterol, has earned the nickname "good cholesterol." That's because it is believed to remove cholesterol from the blood. High levels of HDL in your blood may help to reduce your risk of coronary heart disease. A low level can increase your risk of heart disease.

"Bad"- LDL Cholesterol

Low-density lipoprotein, or LDL cholesterol, is known as "bad cholesterol." Excess LDL builds up in your arteries and may lead to heart disease. The higher the level of LDL, the higher your risk of heart disease. Lowering elevated LDL cholesterol can reduce the risk of having a heart attack.

Helpful Hint

Here's an easy way to remember your levels when you get your cholesterol checked:

You want your HDL to be "high" and your LDL to be "low..." Cholesterol Carewith Beta-Sitosterol and Guggul Lipids has been proven effective in reducing LDL levels... **click here for more information**

What about the ratios?

When the total cholesterol is low, such as in the 150-160 range or less, HDL levels and ratios are essentially insignificant. At such low levels the LDL will also be low, and high or even "average" levels of HDL are not necessary to prevent the buildup of plaque. As the total cholesterol begins to rise, HDL levels and ratios take on more and more importance. So if your total cholesterol is 180, your HDL level and ratio are important. If your total cholesterol is 200, your HDL level and ratio are very important. At 220 or higher they are of extreme importance. Simply put, as the level of total cholesterol begins to exceed 150-160, the HDL level and cholesterol/HDL ratio begins to be a risk factor and gradually increases in importance as the cholesterol count goes higher. You will see this graded increase in the following Cholesterol Risk Chart.

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Cholesterol Care™ Is the Only Guaranteed Supplement That Contains **All Six** Natural Ingredients Proven Effective in Lowering Dangerously High Levels of Cholesterol and Triglycerides...Guaranteed to cut your cholesterol and lower your risk of heart attack or stroke while avoiding costly and often

dangerous prescription drugs. Eliminate worry and health concerns.
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Cholesterol Risk Chart

HDL figures are in the left column. Cholesterol figures are in the top row. Match the row and column.

Total Cholesterol Level

HDL Level	<151	151-160	161-170	171-180	181-190	191-200	201-210	211-220
<21	n/a	n/a	n/a	n/a	n/a	Very High.	Very High	Very High
21-30	Very Low	Very Low			High	High	High	Very High
31-35	Very Low	Very Low	Very Low				High	High
36-40	Very Low	Very Low	Very Low					High
41-45	Very Low	Very Low	Very Low	Very Low				
46-50	Very Low	Very Low	Very Low	Very Low				
51-55	Very Low	Very Low	Very Low	Very Low	Very Low			
56-60	Very Low	Very Low	Very Low	Very Low	Very Low			
61-65	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low		
66-70	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low		
71-75	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	
76-80	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low
81-90	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low
91-100	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low
101-110	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low
>110	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low	Very Low

Cholesterol Care with Beta-Sitosterol and Guggul Lipids has been proven to effectively reduce cholesterol... **Click here for more information**

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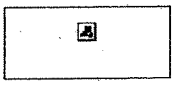

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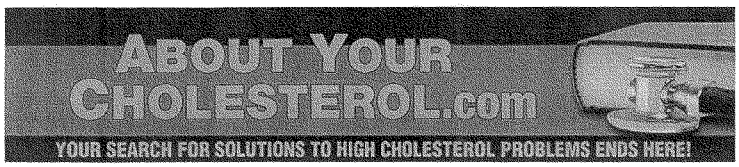

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Natural Cholesterol Reducing Supplements

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- Gugulipid and Cholesterol
- Soy Isoflavones and Lowering Cholesterol
- Red Yeast Rice Extract and Lowering Cholesterol

Foods that Lower Cholesterol

Low Cholesterol Diet Plan

Site Map

AboutYourCholesterol.com

Everything You Need to Know About Cholesterol, High Cholesterol and Ways You Can Lower Total Cholesterol and Minimize Your Risk of Heart Attack or Stroke.

High cholesterol is responsible for 70% of heart disease and is the leading killer of both men and women after the age of 45. High cholesterol leads to arterial blockage, hardening of the arteries, blood clots, clogged arteries, heart attacks and stroke.

On the positive side your cholesterol levels can be controlled and in most cases safe cholesterol levels can be reached and maintained in as few as six to eight weeks. Everything you need to know about lowering high cholesterol to healthy levels including low cholesterol foods, low cholesterol diets, cholesterol lowering drugs, cholesterol charts, cholesterol levels and ways to lower cholesterol naturally can be found on this site.

Here is a Summary of the Topics

Cholesterol 101 What Is Cholesterol?

Bad (LDL Cholesterol) vs. Good (HDL Cholesterol)

Two Sources of High Cholesterol

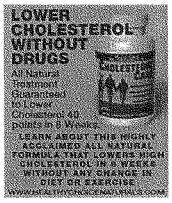
What are Your Risk Factors, Understanding Cholesterol levels?

Cholesterol Testing and Prevention

Cholesterol Level Scale and Cholesterol Risk Charts

Prescription Cholesterol Drugs, the Statin Option

Testimonials



Statin Drugs, Their Benefits and Side Effects

Natural Cholesterol Reducing Supplements

Foods that Lower Cholesterol

Low Cholesterol Diets

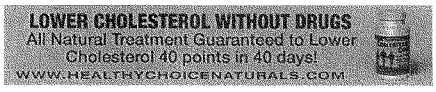
Within each topic you will find both the cholesterol information you need and answers to all your high cholesterol questions. And if you want more in depth information such as cholesterol studies, cholesterol risk charts, statin side effects, ways to lower cholesterol, low cholesterol diets, low cholesterol foods and cholesterol treatment options you will find them all here, quickly and easily.

If you are among those who are affected by high cholesterol due to a family history of high cholesterol or if you have high cholesterol because of unhealthy food choices this site will prove invaluable in providing you with answers, tips, treatments and prevention options that will minimize your high cholesterol concerns and worries.

If you are ready get started on a path to great health and get high cholesterol problems behind you, read-on. You can use the navigation buttons on the left or view our site map to access the many helpful topics and answers to any high cholesterol question you may have.

If you have recently taken a cholesterol blood panel test and already know the problems and risk of high cholesterol you may want to consider this **All natural Cholesterol Treatment** that guarantees to lower high cholesterol by at least 40 points in just 8 weeks or less. It's free of side effects and very affordable.Thousands have found this natural option the right choice for them.

Next: **Cholesterol 101. Get the Basic information you need to understand the causes and types of cholesterol that have an effect on your heart health and risks of serious problems such as heart attack and stroke.**



*These statements have not been evaluated by the FDA. Products not intended to diagnose, cure, treat or prevent any disease.
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Hankin, Joan E

From: Askine, Mark W
Sent: Wednesday, January 16, 2008 7:18 PM
To: Hankin, Joan E; Dean, Robert; Brony, Michael
Cc: Davis, Kristin; Abrams, Thomas W
Subject: Vytorin promotional materials

The action item from our meeting with Drs Temple, Parks, and Colman this evening is that we will inform the sponsor of Vytorin that they need to revise their promotional materials to clearly convey the information about the lack of additional CV benefits with Vytorin compared to Zocor, consistent with the following statement from approved PI for Vytorin: "No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been demonstrated."

We can discuss in greater detail tomorrow. Thanks.

Mark

Davis, Kristin

From: Davis, Kristin
Sent: Thursday, January 17, 2008 2:43 PM
To: Cruzan, Susan M; Temple, Robert; Jenkins, John K; Parks, Mary H; Colman, Eric C; Rosebraugh, Curtis; Zawisza, Julie
Cc: Behrman, Rachel E; Askine, Mark W
Subject: RE: nyt ed > Cholesterol Drug Bombs

These type of letters (asking sponsors to change their promotion) are generally not publicly disclosable. As far as when the changes in promotion will take place, we plan to send the letter by next week and sponsors have until their next reprinting of materials or 90 days, whichever occurs first, to make the changes.

-----Original Message-----
From: Cruzan, Susan M
Sent: Wednesday, January 16, 2008 7:37 PM
To: Temple, Robert; Jenkins, John K; Parks, Mary H; Colman, Eric C; Rosebraugh, Curtis; Zawisza, Julie
Cc: Davis, Kristin; Behrman, Rachel E
Subject: Re: nyt ed > Cholesterol Drug Bombs

Thanks. When is that made public?

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Temple, Robert
To: Jenkins, John K; Parks, Mary H; Cruzan, Susan M; Colman, Eric C; Rosebraugh, Curtis; Zawisza, Julie
Cc: Davis, Kristin; Behrman, Rachel E
Sent: Wed Jan 16 19:02:49 2008
Subject: RE: nyt ed > Cholesterol Drug Bombs

We went over advertising tonight with Kristin, Mary, and Eric, and noted that Vytorin DTC ads did not include that disclaimer (a similar on in Zetia labeling was in ads). We will ask for revision. The reason was that Vytorin does contain a statin drug with such an effect and explaining it all to a lay audience seemed too difficult. We will expect the difficulty to be overcome.

-----Original Message-----
From: Jenkins, John K
Sent: Wednesday, January 16, 2008 11:40 AM
To: Parks, Mary H; Cruzan, Susan M; Colman, Eric C; Temple, Robert; Rosebraugh, Curtis; Zawisza, Julie
Subject: RE: nyt ed > Cholesterol Drug Bombs

We should point reporters to the sentence Mary notes below in the approved labeling.

John K. Jenkins, M.D.
Director, Office of New Drugs
10903 New Hampshire Avenue
Bldg #22, Room 6304
Silver Spring, MD 20993
301-796-0700
301-796-9856 (fax)
NOTE, New E-mail Address: john.jenkins@fda.hhs.gov

-----Original Message-----
From: Parks, Mary H
Sent: Wednesday, January 16, 2008 8:45 AM
To: Jenkins, John K; Cruzan, Susan M; Colman, Eric C; Temple, Robert; Rosebraugh, Curtis;

Zawisza, Julie
Subject: RE: nyt ed > Cholesterol Drug Bombs

To misstatements. In fact, Vytorin label (which is simvastatin plus ezetimibe) has the following sentence under Clin Studies:

"No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established"

-----Original Message-----
From: Jenkins, John K
Sent: Wednesday, January 16, 2008 8:00 AM
To: Cruzan, Susan M; Colman, Eric C; Temple, Robert; Parks, Mary H; Rosebraugh, Curtis; Zawisza, Julie
Subject: RE: nyt ed > Cholesterol Drug Bombs

Susan

I think for now you need to say that:

-We need to review the data from the ENHANCE study once it is submitted to FDA so we can more fully understand the results

-We will be considering what, if any, impact this new study will have on our standards for approval of cholesterol lowering drugs and may seek outside input at a future public meeting

-Zetia and Vytorin were approved based on their proven ability to lower cholesterol, which the Agency has accepted as a validated surrogate endpoint and has been the standard for initial approval of other cholesterol lowering drugs, including statins

-Zetia and Vytorin do not carry claims for reduction of cardiovascular events other than y claims that may have been demonstrated for the statin that is used in combination. ..y claims for reduction of cardiovascular events above and beyond those of any statin used in combination would require clinical trials like those that are ongoing. This same approach, i.e., initial approval based on LDL lowering followed by later studies to demonstrate reductions in cardiovascular outcomes, has been used for other cholesterol lowering drugs, including statins.

Mary and Eric should review the above to make sure that I have not misstated anything.

John

John K. Jenkins, M.D.
Director, Office of New Drugs
10903 New Hampshire Avenue
Bldg #22, Room 6304
Silver Spring, MD 20993
301-796-0700
301-796-9856 (fax)
NOTE, New E-mail Address: john.jenkins@fda.hhs.gov

-----Original Message-----
From: Cruzan, Susan M
Sent: Wednesday, January 16, 2008 7:44 AM
To: Colman, Eric C; Temple, Robert; Parks, Mary H; Rosebraugh, Curtis; Jenkins, John K; Cruzan, Susan M; Zawisza, Julie
Subject: Fw: nyt ed > Cholesterol Drug Bombs

reness. We have had queries from a fair number of media outlets who are asking about ...e approval for this drug and how this impacts how we view continued use of this drug and related advertising. I sent a query yesterday.

We have advised reporters that
we will have to review all data in light of studies to determine if it impacts the

labeling and advertising for the drug.

Susan C

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Conover, Eileen (HHS/OS) <eileen.conover@hhs.gov>
To: Brodsky, Jason D; Weems, Kerry (CMS); Pearson, Christina (OS); Zawisza, Julie; Babin, Holly (OS); Meron, Daniel (OS); Cruzan, Susan M; Stannard, Paula (OS); Hall, Bill (OS); Ott, Laura (OS); Bennett, Jason (OS); Nelson, Michael K (OS); Ventimiglia, Vince (OS); Hughes, Matt (OS); Lawrence, Arthur J (OS); Mckeown, Rich (OS); Burton, Craig (OS); Winckler, Susan; Sasse, Ben (OS); Mitchell, Brian P (OS); Lutter, Randall; von Eschenbach, Andrew C.; Barnett, Brynn A (OS); Morris, Greg (OS); Campanelli, Richard (OS); O'Neill, Jim (OS); Sass, Raymond (OS); Parekh, Anand (OS); Schweers, Kevin (OS); Pearson, Christina (OS); Wright, Don (OS); Stansel, James (OS); O'Neill, Jim (OS); Sundlof, Stephen F; Dunham, Bernadette M
Sent: Wed Jan 16 07:14:01 2008
Subject: nyt ed > Cholesterol Drug Bombs

January 16, 2008

Editorial

Cholesterol Drug Bombs

There have long been suspicions, but it was still very disturbing to learn this week that a heavily promoted cholesterol-lowering drug had flunked a clinical trial of its effectiveness in reducing fatty deposits in arteries. The two companies that reap billions from the drug had been cynically sitting on the results for more than a year.

The drug, Zetia, and a combination pill that contains it, Vytorin, are made by Merck and Schering-Plough and used by millions of patients. They generated more than $5 billion in sales last year. The companies sponsored a clinical trial of the drug's effectiveness in hopes that positive results would strengthen their marketing efforts.

The trial was conducted in 720 European patients with genes that cause abnormally high cholesterol levels. For two years, the patients received either Zocor, an older cholesterol drug, or Vytorin, a combination of Zocor and Zetia. The assumption was that Vytorin would reduce the growth of fatty plaques — a risk factor for heart attacks and strokes — more than Zocor alone. As it turned out, the plaques grew almost twice as fast in patients taking the Vytorin.

There are reasons to be cautious about interpreting these results. The number of patients was relatively small. And many of them may have used different drug treatments for years before entering the trial, possibly diminishing the effectiveness of adding Zetia.

The companies' grudging release of the data has raised disturbing questions. A House committee will explore whether they withheld the results lest they interfere with sales and only released them under pressure from Congress and news media reports. Whatever the committee discovers, the experience is one more argument for why scientists involved in studies sponsored by drug companies must insist on the right to review and release data. A new law that strengthens the penalties for companies that do not release data promptly should help.

The findings also raise doubts about the current belief that lowering cholesterol is the key to cardiovascular health. The study showed that Vytorin reduced bad cholesterol significantly more than Zocor alone. The problem was that it failed to reduce the formation of plaque.

The companies are conducting three large clinical trials to test whether Vytorin can nevertheless reduce heart attacks and strokes. Results won't be available until at least

2011. Meanwhile, with no evidence of effectiveness in plaque-reduction, it seems clear that Zetia and Vytorin should be used sparingly, in cases where all other cholesterol drugs have failed.

Eileen Conover

Office of the Chief of Staff

Ph: 202-690-8157

Fax: 202-205-2405

From: DeGroot, Eric [e.degroot@imagepace.com]
Sent: Wednesday, March 15, 2006 7:08 PM
To: M.Gene Bond; J.J.P. Kastelein; daniel.o'leary@caritaschristi.org; Strony, John; Bransford, Toni; j.polack@imagepace.com
Subject: RE: Batch Reading Discrepancies

Attachments: Document2.pdf

dear gene,

I am not neglecting the important contributions of all and certainly not yours.
I
However in the course of Enhance there has been little anticipation on the things to come prior to the efficacy analysis and things were simply not sorted out prior to start of that efficacy analyses.
This is a major logistic error and includes the complete lack of quantitive In-Trial QAQC data.
I have requested alterations in course for over 3 years, and now time has caught up.

At CEL we have been treated like bunch of criminals.
We have been harmed.
The data has been designated as 'crap' and the variability is 'very bad'

Starting too late (in October 2005) with the efficacy phase with an ever increasing number of readers, with no time to spare, is another major logistic failure.
All of this has been indicated by me repeatedly.

The complete lack of smooth feed back loops in the course of the trial has created a logistic disaster that could have been prevented elegantly.
That has also been repeatedly communicated.

The thing is: actually I do not blame you.
The thing is, you could not know nor do many people at SP, because for running this trial you need to 'zoom in' and 'out' from overview to the very detail of the study in order to make important decisions .
For that you need to constantly monitor and work with descriptive statistics in order to keep the bookkeeping of the trial in order.
You also need a quantitative tool: quantitative data.
The only way to do this and provide for proper QC is efficiently monitor the data quantitatively as Jo Polak indicated below: only assessment of the primary endpoint data are the proof of things going right and things going wrong.

The fact that you told me that you are unable to do the statistics nor posess over data has made my life very, very difficult.
It basically means you are unable to grasp the scope and magnitude of 50000 images, let alone handling them.
You do not have a 'feel' with the data.

As a consequence your advices are not wrong, they are logic and bright and I always find your discussions meaningful and helpful.
However due to sheer size and magnitude your advices lack reality testing and insight in the process of running this trial one can only acquire by bookkeeping and calculation.
This bookkeeping is what you do not do and cannot do, because adequate quantitative data are missing.
That is your problem and that makes you partially inadequate to cope with specific issues of this study.
Since I do a lot of studies with same protocol I also miss the data, but the difference is that I know what I am missing and I have been yelling it from the rooftops.

At present we are again 1 month underway using a system I think will work better and will get us on the road better prepared.
I think the side-by-side assessment is an excellent idea.
As time goes on, again time is catching up and this may be the pitfall like it has been

before.

We at CEL are working hard to adapt to the 'new' side-to-side approach and make things happen.
We are not awaiting orders, we are not talking endlessly, we do await simple decisions, we do not await payment, we are not frustrated, but anticipate and enthousiastically have started till we hear from SP.
The first phase of our replicates according to the new and old method is underway and we will have more data by the start of next week.
This will save the time we will so dearly need at the finish.

Finally, the overall variability of the replicates has been calculated as an SD of 0.09mm, even without taking out the extremes/outliers the software system is designed to cope with in the first place.
The outcome is consistent and robust.
Less then half the magnitude of the anticipated SD of 0.20.

my best regards
eric

eric de groot, md phd
+31 6 5160 9046

From: M.Gene Bond [mailto:mgbond@wfubmc.edu]
Sent: Wed 15-Mar-06 4:53 PM
To: DeGroot, Eric; J.J.P. Kastelein; daniel.o'leary@caritaschristi.org; john.strony@spcorp.com; toni.bransford@spcorp.com; j.polack@imagepace.com
Subject: RE: Batch Reading Discrepancies

Eric; Was working on your written "contributions" to the amended ENHANCE reader protocol, and the re-training agenda for your readers when your latest e-mail message was opened.

Your question is "any thoughts?". You are misinformed about my advice to SP concerning independent "advisors". You are incorrect in stating that the ENHANCE trial is "in great trouble" due to my advice. In fact Eric, you have in past conversations belittled, attacked, and degraded significant contributions made by several of your collaborators in this project, including professionals in the Coordinating Centers, Sponsor's and even a senior member of your staff. The people who have tried to assist you and your lab in meeting the high scientific standards required in this study have received the back of your hand, and your arrows. Your attitudes and methods of expressing your frustrations continue, even though your peers have contributed significantly to helping you write training agendas, certification proceedures, ect., i.e., things you either would'nt or could'nt write. Lastly, the Qualitative Assessment that you indicated "(flunked completely) ", contains the majority of Sonographer controlled performance characteristics that influence the variability of IMT measurements. Based on Johan's readings, compared with the original efficacy reads, your readers were not fully trained to evaluate these Sonographer controlled performance characteristics. That is a failure to implement an agreed upon protocol. Gene

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From: DeGroot, Eric [mailto:e.degroot@imagepace.com]
Sent: Tue 3/14/2006 5:53 PM
To: J.J.P. Kastelein; M.Gene Bond
Subject: RE: Batch Reading Discrepancies

Dear Gene,
There seems to be a great discripancy in the ideas about image assessments.

At present you have heavily payed entered the SP trial in great trouble due to your advices that include:
1. Independent advisors (Hennig, PI), that very expensively have taken away quality assessment.
2. Qualitative assessment (that flunked completely) Any thoughts?
Best regards
Eric

-----Original Message-----
From: Polak, Jo
Sent: Fri 10-Mar-06 6:19 PM
To: Brown, Mike; DeGroot, Eric
Cc: Zabbatino, Salvatore
Subject: RE: Batch Reading Discrepancies

Look at the data we have. The bottom Line is the ability to do the imt measurement and draw the line. The image quality score is a rough surrogate.
At least that is the intent of having implemented and using such a score.
Jo

---Original Message-----
From: eric de groot [mailto:ericdg@xs4all.nl]
Sent: Wednesday, August 23, 2006 4:41 PM
To: Strony, John
Cc: J.J.P. Kastelein
Subject: RE: sp efficacy analysis qc

I already used this approach in the VFS.
This supported you as well it supported Toni.
Thats's why it worked in the compare with Imagepace and it will save your ass when the product doesn't show an effect.
Be careful with me my dear John.
Eric

From: Strony, John [mailto:john.strony@spcorp.com]
Sent: Wednesday, August 23, 2006 6:48 PM
To: Bransford, Toni; eric de groot; M.Gene Bond
Cc: Petrauskas, Stanley; Onno Bakker; Veltri, Enrico; J.J.P. Kastelein
Subject: RE: sp efficacy analysis qc

Eric,

The CEL did a great job with the Vanguard reading exercise. To your credit, the MSP joint venture attributes to a great degree the remarkable reduction in the observed variability to your single handed efforts at overreading and QC'ing the control images. The problem is that with the credit comes the expectation that you personally will continue to demonstrate this commendable level of ownership and leadership. There is much at stake with this study. As such the joint venture will not allow senior reader(s) or designee(s) to perform the task that you so masterfully do.

Look at it this way, you will much to celebrate this New Year's holiday.

John

-----Original Message-----
From: Bransford, Toni
Sent: Wednesday, August 23, 2006 11:20 AM
To: 'eric de groot'; M.Gene Bond
Cc: Strony, John; Petrauskas, Stanley; Onno Bakker; Veltri, Enrico
Subject: RE: sp efficacy analysis qc

As we discussed yesterday, there is NO WAY that SP or the joint venture will agree to having observers "over-reading" the readers. The observers will not be paid for and their costs are being deducted from the budget to be sent back to you if it has not been already. You can continue to try to sneak in things that we have already precluded, however, we will not relent and allow for anyone other than yourself as "observer" or "over-reader" or "super-reader" or post-reader" or whatever term is being used at the moment. It stands for the same thing...that is someone other than you doing the QC. Once again, I admonish you to stick to the terms predefined. I have rewritten the SOP to make it more agreeable to your sponsors. This was discussed yesterday and has been discussed numerous times in the past 6 months. There will be no compromises here.

Toni Bransford, MD, FACC, FASE
Clinical Project Director
Schering-Plough Corporation
908-740-2551

Subject: Fw:

FYI, good news I assume

Soren Christiansen

-----Original Message-----
From: J.J.P. Kastelein <j.j.kastelein@amc.uva.nl>
To: 'Strony, John' <john.strony@spcorp.com>
CC: Christiansen, Soren Bo (WS); Rick Veltri <enrico.veltri@spcorp.com>; 'Bransford, Toni' <toni.bransford@spcorp.com>
Sent: Tue Dec 12 10:12:39 2006
Subject:

Dear John,

As promised, I spoke at lenght last night with Dr. Steve Nissen about the submission date for the final data of the ENHANCE study.
He has promised to give me a prominent spot in the late breaking trial session of the ACC meeting in New Orleans. Furthermore, he would allow a later date than the 3rd of January for the data-submission.

This is great news, since it means that there is no reason what so ever to let anything stand in the way of an ENHANCE presentation in New Orleans.

Kind regards, John

****
Joyce Jansen
P.A. to John J.P. Kastelein, MD, PhD
Professor of Medicine
Chairman, Dept. of Vascular Medicine
Academic Medical Center
Meibergdreef 9, room F4-159.2
1105 AZ Amsterdam, The Netherlands
tel: +31 20 566 6612
fax: +31 20 566 9343
mail: j.j.kastelein@amc.uva.nl / j.s.jansen@amc.uva.nl

From: Christiansen, Soren Bo (WS)
Sent: Monday, January 15, 2007 8:25 PM
To: Stoner, Elizabeth; Pasternak, Richard; Musliner, Thomas A.; Nouss, Edgar M.
Subject: FW: ACC
As promised
Soren

From: J.J.P. Kastelein [mailto:j.j.kastelein@amc.uva.nl]
Sent: Monday, January 15, 2007 4:31 AM
To: Christiansen, Soren Bo (WS)
Subject: ACC

Dear Soren,

If it is up to me, I definitely want to present ENHANCE at the ACC in New Orleans but bigger forces than myself are at work here so the outcome of that is unknown to me as well.
Everything will depend on how things are going this week. A large group from SP international as well as local is visiting my department to determine if and how many of the images will have to be re-read.
Also, an outside IMT-specialist as well as an additional data-manager will be added to our team. So all in all, at the end of this week we will know whether we can make ACC or not.

Kind regards, John

****

Joyce Jansen
P.A. to John J.P. Kastelein, MD, PhD
Professor of Medicine
Chairman, Dept. of Vascular Medicine
Academic Medical Center
Meibergdreef 9, room F4-159.2
1105 AZ Amsterdam, The Netherlands
tel: +31 20 566 6612
fax: +31 20 566 9343
mail: j.j.kastelein@amc.uva.nl / j.s.jansen@amc.uva.nl

Schering Plough ENHANCE consultancy report

Michiel L. Bots, MD, PhD
Associate Professor of Epidemiology
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Heidelberglaan 100, 3584 CX Utrecht
The Netherlands
m.l.bots@umcutrecht.nl

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Summary

The CIMT measurements seem to be done according to the procedures outlined in the protocol. The CIMT measurements in ENHANCE have been done in a consistent manner, leading to reproducibility findings that compare well with that of published studies from other multi-centre randomized trials. The number of missing data points is most likely somewhat higher that what has been reported earlier. Yet, the evidence shown to me is sufficient to indicate that the CIMT data in ENHANCE are fine: i.e., no better, no worse than what has been reported in the literature.

However, the SP/MSD team would like to their utmost to potentially further reduce the measurement variability in the data, given the restriction of the availability of the imaging information. Based on the information there might be three ways to address that. Firstly, reduction of missing CIMT values by evaluating whether CIMT can be validly measured from other image selections of the same visit. Secondly, a longitudinal outlier analyses, i.e. identification of the outlier, re-evaluation, and potentially change the CIMT value in the dataset. Thirdly, optimise the statistical analyses of the data, i.e., use the state of the art model statistical models to assess difference in change in CIMT across treatment arms in randomised controlled trials.

Important to realise is that the above mentioned activities might reduce measurement variability to some extent. The expected effects on variability are however likely to be modest. Again, randomisation in ENHANCE protects against bias in the estimate of the difference in CIMT change between treatment arms.

1. Introduction

During a recent telephone conversation between members of the Schering Plough team of the ENHANCE study, among which Toni Bransford and John Strony, the SP/MSD team would like to have dr. Bots as an independent consultant for advice regarding CIMT issues in the ENHANCE trial.

ENHANCE is a randomised controlled trial evaluating the combination of Ezetimibe + simvastatin versus simvastatin alone on progression of carotid intima-media thickness as assessed with ultrasound.

From the conversation, the following was understood

- The study is still in its blinded phase. The timeline to de-blinding of the study has been extended until several issues are resolved.
- The design of the ultrasound component of ENHANCE had 7 visits in which CIMT was assessed (femoral IMT and distal common carotid M-mode was measured as well, but since CIMT is the primary endpoint, in this document CIMT will be discussed only).
- Visits included a duplicate baseline assessment, a duplicate assessment at 12 months (sample), a single assessment at 18 months and a duplicate assessment at the end of the study.
- The ultrasound images provided to the core laboratory were a single still frame of the far wall of the right common carotid segment, a still frame of the far wall of the right bifurcation, a still frame of the far wall of the internal carotid segment, and three similar images obtained from the left carotid. In total a maximum of 6 images were provided to the core lab for CIMT measurement at each visit. There is no additional image information available (for example clip or a videotape).
- The reading protocol indicated that the images of e.g. the right common carotid of all the 7 visits were displayed on one PC screen so that all images should be read simultaneously. This approach should enhance comparability in the readings. Furthermore, the approach should identify images where measurements should be performed on that were clearly different in anatomy from the other images. In ENHANCE angles information was not available.
- For each visit the CIMT values of all six segments are averaged to provide an aggregated CIMT value for each visit. Next, the aggregate CIMT values from

the duplicate visits (baseline and end of study) are averaged. Duplicate visits are Visits 3, 4 and 13, 14 (baseline and endpoint). In a randomly selected subset of subjects, an additional IMT ultrasound image will be performed one week after visit nine as part of a quality control program to ensure standardization of image acquisition and analysis.

- The primary outcome variable in ENHANCE is change in CIMT between baseline (visit 3-4) and end of study (visit 13-14). CIMT is the average of all at least four mean CIMT values measured from the image.

Questions that arose from the SP/MSD team dealt with whether or not the reading protocol was actually closely followed during the reading process. Secondly, the data that were available to SP showed sometimes large CIMT differences between visits, (sometimes large differences between visits 1 week apart). These differences were beyond what was to be expected from normal progression. The main question was what should be done with these differences. So this leads to the main two objectives.

2. Objectives

1. Has the reading of the ultrasound images been done according to the procedure outlined in the protocol?
2. How can the 'outliers' be addressed in an adequate manner before de-blinding of the study occurs?

3. Methods

- Three meetings were set up in Amsterdam at the core lab to address these issues. One on Tuesday, 16 January 2007 from 13.00-15.00 and one one Thursday, January 18, 2007 from 12.00 -13.00 hours, and one on Thursday, January 18, 2007 from 13.00-15.00 hours.
- During these meetings information should become available to fully address and discuss the objectives.
- Bots will develop the questions and will provide a written report.

4. General aspects regarding the objectives

Has the reading of the ultrasound images been done according to the procedure outlined in the reading protocol?

During the planned meetings, the core laboratory needs to provide the information on how the images have actually been read. A presentation would suffice.

In addition, information should be given about the process of the procedures installed when a selected image does not match the anatomical segment of what has been requested. For example, when a far wall right common carotid artery image is requested, and the image provided is actually the far wall of the right bifurcation. In general, three ways are present to deal with such images; (1) when possible, request re-scanning of the participant; (2) measure the image anyway, and use the measurement in the estimate of the primary endpoint; (3) leave out the image in the measurement procedure (missing). These approaches should be outlined in the imaging/reading protocols of the study.

The best solution would be the request of rescan of the participant. The second best is to have a judgement call by the reader to indicate how the selected image actually deviates from the other images based on the anatomical image information and to what extent the deviation is expected to affect the measured CIMT. When deviations are small (i.e., the CIMT is likely a good reflection of what the CIMT in the segment is expected to be), measurement should provide a good estimate of the CIMT value; when the deviation is considered large (a totally different segment with a priori expectation of thicker/ thinner CIMT value), a 'no measurement' is appropriate. The third solution, i.e., a priori perform no measurement, may lead to having more missing values for that measurement than needed.

The effect of missingness of CIMT information on the progression rates and on the ability of finding a treatment difference is here of importance. Since the study was blinded for the treatment, and the sonographer can not identify which participants are 'progressors' and which participants are 'regressers', the effect of missing imaging information is likely to be a random phenomenon. This is unlikely to affect the mean progression rate in the group, but may reduce the precision of the progression estimate a little. The latter may reduce to some extent the ability to detect differences between groups, although the magnitude of the difference between the groups is expected to be correct.

How can the 'outliers' be addressed in an adequate manner before de-blinding of the study occurs?

An 'outlier' is a CIMT value that is clearly different from other CIMT values for a similar segment (or for the primary outcome) that have been measured in a time sequence. For example, in one participant a common CIMT value of 0.70 mm measured at first baseline visit, a common CIMT value of 1.50 mm measured two weeks later, and a common CIMT value of 0.71 mm measured after 12 months, and a common CIMT of 0.75 mm measured at 13 months. The same may apply to the aggregate CIMT value; an aggregate value of 1.25 mm, 1.70 mm, 1.20 mm and 1.18 mm, respectively. Note that outliers can also go into the other direction: 1.25 mm, 0.80 mm, 1.20 mm and 1.18 mm.

The contribution of an 'outlier' on the study findings depends on what the primary outcome CIMT is. For example, when the primary outcome in a trial is difference in progression of the aggregate CIMT, and when the primary outcome is based on the average of 6 CIMT values, the first example outlier will lead to a contribution of an outlier to the observed CIMT aggregate of (1.50 mm- 0.70 mm)/6 = 0.133 mm. The aggregate CIMT of that visit will be overestimated with 0.133 mm. An outlier of 0.30 mm, contributes 0.05 mm to the aggregate, which is within the reproducibility range. This reasoning shows that only considerable outliers potentially affect the final CIMT estimate of a certain visit.

An outlier may be due to (1) a real biological process, e.g. a haemorrhage in the arterial wall at the location of the measurement (found in 2-4% of the participants); (2) a CIMT measurement from an image that shows a different anatomical location (imaging problem) and (3) a mistake in the reading of the image (reader problem).

There are different ways to identify an outlier. It can be done on segment specific measurements of all the visits or on the aggregate CIMT value for each visit. Since the aggregate is the main variable of interest, which also shows less variability from visit to visit as compared to segment specific values, it might be more appropriate to use the aggregate for assessment of outliers. To the best of my knowledge there have been no published reports that provide a recommendation for assessment of outliers. One of the approaches that has been taken in one of the trials (three years, 9 CIMT measurements) I have been involved in was to calculated the mean of all the aggregate CIMT estimates of all visits (study mean). Next, calculate for each visit the difference between the visit CIMT and the mean of all the aggregate values during

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study (study mean) and take one 20% upward and downward from that mean as being an outlier. In this study, 20% difference reflected around 0.20 mm difference in aggregates between visit specific values and the overall study mean. Of the identified outliers examine all the CIMT values of the segments to identify the potential CIMT value that is actually responsible for the outlier.

Another possibility that may be used in ENHANCE may be to use the duplicate baseline and end of study data to identify on segment level those measurements that for example differ more than 50% among each other. A potential down side is that you miss the longitudinal aspect of outliers since you do not relate the baseline value with 12 month, 18 month and end of study measurements.

Finally, one may also use the reproducibility data of the mean absolute difference in the aggregate CIMT (0.03-0.05 mm) and define an outlier based that value plus and minus 2 or 3 times the standard deviation of the arithmetic mean difference of the aggregate CIMT value. Given that the standard deviation of the arithmetic mean difference of an aggregate is around 0.06-0.010, this approach would lead to identification visits that difference 0.03-0.05 mm +/-0.12 – 0.30 mm from the overall study mean.

What approach is taken to define an outlier, there are no standards, and the choice remains arbitrary. It is usually a balance between workload, time and costs and estimates of potential benefit for the data. The latter is difficult to judge, and one has to rely on reproducibility data as collected in the study. ENHANCE is unique here in having duplicate measurements at two time points and great potential to evaluate the effect of the outlier procedures.

When an outlier has been defined, the evaluation may indicate that is it is a real morphological change (accelerated progression of atherosclerosis, haemorrhage) or 'measurement error'. The latter comprises ultrasound protocol deviations (scanning wrong vessel or wrong segment) or image reading errors (measuring ultrasound imaging artefacts, difficult atherosclerotic plaques, or inaccurate boundary tracing). Morphological changes do not need any action. The measured CIMT is correct, and remains in the database. Reading errors need to be corrected. So the image is re-read and the CIMT value of the re-read image is being used in the final dataset. Ultrasound protocol deviations constitute a different problem. When possible, another image may be selected from clips or videotapes and read. However, in ENHANCE

this is not available. Thus the solution chosen may be is to have a judgement call by the reader to indicate how the selected image actually deviates from the other images based on the anatomical image information and to what extent the deviation is expected to affect the measured CIMT. When deviations are small (i.e., the CIMT is likely a good reflection of what the CIMT in the segment is expected to be), measurement should provide a good estimate of the CIMT value; when the deviation is considered large (a totally different segment with a priori expectation of thicker/ thinner CIMT value), a 'no measurement' is appropriate.

The effect of having missing imaging data (due to lack of compliance of the imaging protocol) depends on whether missing images/readings affect the CIMT progression rate and whether it affect the ability to detect differences between treatment arms.

Missingness of CIMT data only affects progression rates when missingness is related to factors that determine the CIMT progression rate. This can be easily examined in the existing blinded dataset given the basic assumption in a blinded dataset that the risk factor relations are stronger that any treatment effect. Using the group with complete data, one can study the relation between baseline risk factors and CIMT progression. From these analyses, factors that are related to an increased or decreased progression can be identified. Next, one may evaluate whether these factors are different among subjects with missing values due to imaging aspects.

Since the study was blinded, and the sonographer can not identify which participants are 'progressors' and which participants are 'regressers', the effect of missing imaging information is likely to be a random phenomenon.

5. Results based on discussions and material provided

Has the reading of the ultrasound images been done according to the procedure outlined in the protocol?

During the meeting of Tuesday, the core lab showed how measurements were done. These were indeed done in a manner that was described in the protocol. The core lab indicated that when of the 7 images there were one or two that were clearly distinct from the others, in terms of anatomy, no measurements were done, and no CIMT data came in the data base.

Of note is that when a 'no-measurement' was seen for a given segment there was not a systematic attempt to check where an CIMT could be read from another image

of the same visit. For example, when a far wall bifurcation of a participant during visit 13 could not be measured due to anatomical differences and/or wrong imaging, there was no attempt to check whether a bifurcation far wall CIMT might be measurable from the CCA or ICA selections at that visit.

How can the 'outliers' be addressed in an adequate manner before de-blinding of the study occurs?

Before the discussion on outliers starts, first the reproducibility of the data needs to be evaluated. This included reproducibility data from visits 3-4 and from visits 13-14 and indicated that the reproducibility of CIMT (the entire process including variability due to imaging and reading) is excellent in this study. The Intraclass correlation coefficients were high, the mean CIMT differences between visits and their corresponding standard deviations were small. The same applied for the mean absolute CIMT difference and the standard deviations. These data are well in line with studies that have been published in the literature. Based on these findings there seems to be little concern regarding the validity and precision of the data.

Yet, the SP statistician sees in the segment specific data large differences that are considered beyond 'biological variation'. Based on these findings, I have checked in one of our datasets obtained from a randomised controlled trial the variation we found in the maximum CIMT measurements of the far wall bifurcation. Our data strongly resemble the ENHANCE data in terms of the magnitude in differences in CIMT values between visits.

The core lab has re-evaluated all the images of the visits 3-4 that had a CIMT value that was 50% of more different. The re-evaluation dealt with new evaluation, re-reading, and possible setting to 'no- measurement'. A similar exercise was done for the visits 13-14. Next, the statistician evaluated how the reproducibility based on the original data changed when the 'corrected' outlier data were used. This improved in particular the standard deviation of the mean differences. Yet, the improvement was very modest.

Of note is that this outlier exercise did not evaluate longitudinal outliers based on differences between visits 3-4 and visits 13-14, but only 'cross-sectional' outliers.

The SP statistician indicated that there was concern with missing data. Of the common carotid segment CIMT was missing for 4% of the participants, for the

bifurcation segment 12% and for the internal segment 12%. This is higher than in the studies of the consultant but in line with observational studies. However, the ultrasound protocol used by the consultant are much more extensive in terms of collecting imaging information, and therefore allows for obtaining CIMT information from other sources when the selected images are too poor.

In the discussion two aspects came up: First can we reduce the missing data?, and second does this affect the CIMT estimate of the visit?. The only approach of a reduction of missing data is to check whether information on CIMT can be validly collected from other selections of that same visit. This has not been explored by the core lab, and a pilot on feasibility might be useful.

Missingness may affect the CIMT value. Yet, the current statistical models that are used in the analysis of CIMT trial data do appear to take care of that in an adequate manner. The current approach to analyse CIMT progression trial data is a multi-level, repeated measures linear mixed effects model. Levels used for the data are usually subject, and carotid artery site within subject, and the repeated measure was time. The model may be specified in terms of fixed effects for carotid artery site, age, sex, reader, ultrasound machine, randomized treatment group, time, and the interaction of randomized treatment group and time. Time is a continuous variable, and is the interval in years from date of randomization to date of CIMT measurement. Random effects within the model are intercepts and slopes, for subjects, and sites-within – subjects. The dependent variable is measured CIMT. Differences in annualized change between the 2 randomized treatment groups are tested by evaluating the statistical significance of the time-by-treatment interaction term. A feature of the model is that it fits regression lines to profiles of CIMT values, consisting of pre-randomization values, values from visits during the treatment period, and values from end-of-study visits. If a subject withdrew with an incomplete profile after the first post-randomization ultrasound visit lines can still be fitted to the data available. Unfortunately, in the ENHANCE statistical protocol a different approach has been taken, which is based on averaging of the values. Since that approach is suggested to be less powerful and more susceptible for bias (due to missing data), the present statistical approach might need some re-consideration.

Of note is to realise that this is a randomised controlled trial, the features mentioned above affect both treatment arms. In general, missingness and outliers affect the precision of the CIMT progression estimate, and may affect the ability to

detect a difference in CIMT progression between the treatment groups. How large that effect is can not be determined validly.

Finally, the SP statistician indicated that the lentgh of the CIMT measurement introduces variability. Apparently, there are some subjects in which the length of the tracings differs between visits, which may have a profound effect on the mean CIMT value from that image. The only solution I can suggest is to use the maximum CIMT rather than the mean value CIMT of an image. One has to realise, however, that the reproducibility of a single segment specific maximum CIMT measurement is generally lower than that of a segment specific mean CIMT measurement. The reproducibility of an aggregate based on maximum CIMT measurements may not be very different from that of an aggregate based on mean CIMT measurements. The advice would to evaluate this further in the current blinded dataset, not by using individual segment data but by using the mean maximum aggregated CIMT values.

6. Conclusion / recommendation

The CIMT measurements seem to be done according to the procedures outlined in the protocol. The results from the reproducibility study showed that the CIMT measurements have been done in a consistent manner, leading to reproducibility findings that compare well with that of published studies from other multicenter randomised trials. The number of missing data points is most likely somewhat higher that what has been reported earlier. This can be attributed to having only one image for CIMT analysis. Yet, the evidence to me is sufficient to indicate that the data are fine.

However, the SP/MSD team would like to their utmost to potentially further reduce the measurement variability in the data given the availability of the imaging information. Based on the information present, there might be three ways to address that. Firstly, reduction of missing CIMT values by evaluating whether CIMT can be validly measured from other image selection at the same visit. Secondly, a longitudinal outlier analyses, i.e. identification of the outlier, re-evaluation, and change in the dataset. Thirdly, optimise the statistical analyses of the data as indicated above.

The definition of an outlier is based on the findings of the reproducibility study. The parameters to use are the mean absolute difference between visits 3-4

measurements (e.g. 0.03 mm), and the standard deviation of the arithmetic mean difference between CIMT values of visits 3-4 (e.g. 0.06). An outlier may then be defined as present when a difference in CIMT values between the visit 3, visit 4, visit 13 and visit 14 values is above or below 0.03 +/- 3*0.06 = a value above or below 0.21 mm.

Important is to realise that the above mentioned activities might reduce measurement variability to some extent. Since this is expected to involve only a small number of the measurements, the expected effects on variability are likely to be modest. Again, randomisation protects against bias the estimate of the difference between treatment arms.

From: Bova, Alice
Sent: Monday, June 18, 2007 9:50 PM
To: 'M.Gene Bond'; Strony, John; Petrauskas, Stanley
Cc: ericdg@xs4all.nl
Subject: RE: Enhance and the decision today

Gene

Let me try and discuss the publication process for the Merck/SP Cholesterol JV. There is a full MSP JV group that works on publications and the publication plans as well as presentations. All intended publications will go through appropriate OC members for review. In fact both you and Eric are listed as authors with Prof. Kastelein as the lead author on the publications.

There are three publications planned for ENHANCE:

Certification paper (which is what you sent) Baseline paper Primary Results paper

In all three cases, a writer was assigned to these publications after discussion and endorsement with Prof. Kastelein, Dr. Strony and Dr. Veltri. The selection of the target journals for all three publications was also endorsed by Prof. Kastelein, Dr. Strony, Dr. Veltri and the MSP JV pub team.

The Certification paper is currently under revision and is intended for JAAC, preferably prior to the release of the primary results paper.

The Baseline paper is being drafted with available blinded data, but of course will need the baseline IMT data to complete the paper. The intended journal for the baseline paper is AJC. Again, the goal is to publish the baseline paper prior to the primary results paper. If we run out of time, the baseline paper may not be submitted.

The primary results paper is also being drafted with general information and will be pending the release of data to complete. The shell will be sent for review to expedite the final review of the paper once we have data. The target journal is LANCET with hopefully on line publication at the time of AHA 2007.

The abstract for AHA is a shell with out data and will be sent to AHA for the late breaker (deadline 29Jun07, 5 pmEST).

The presentation will also be created by the MSP JV Publication team working closely with Prof. Kastelein who will be the presenter at AHA.

This is the MSP JV process. Since the OC is working diligently on the data for the study, publications was never a high priority for the OC agenda, hence the need for more ad hoc discussions outside the normal OC meeting. If you have concerns regarding OC role, I would recommend discussing this directly with Dr. Strony or a small group in an ad hoc meeting.

Please let myself, Stan or John what other steps should be taken to ensure the OC is in the loop for the publications.

Best regards,

Alice M. Bova
Associate Director, Global Project Management Schering Plough Research Institute Phone 908-740-4208 Fax 908-740-3621 alice.bova@spcorp.com

-----Original Message-----
From: M.Gene Bond [mailto:mgbond@wfubmc.edu]
Sent: Monday, June 18, 2007 02:53 PM
To: Bova, Alice; Strony, John; Petrauskas, Stanley
Cc: ericdg@xs4all.nl

Subject: FW: Enhance and the decision today

Hi Alice, Please find attached a draft manuscript for the initial reporting of reproducibility in the ENHANCE study. The development of this manuscript was approved by the Operation Committee. Can we discuss the approach to publications? Gene

---

From: ericdegroot [mailto:ericdg@xs4all.nl]
Sent: Mon 6/18/2007 1:45 PM
To: M.Gene Bond
Subject: RE: Enhance and the decision today

-----Original Message-----
From: M.Gene Bond [mailto:mgbond@wfubmc.edu]
Sent: Monday, June 18, 2007 7:25 PM
To: ericdegroot
Subject: RE: Enhance and the decision today

Sorry Eric, The Medical restricts my ability to open the files you sent.
Canyou make them available in an pdf format? Gene

From: ericdegroot [mailto:ericdg@xs4all.nl]
Sent: Mon 6/18/2007 1:09 PM
To: M.Gene Bond
Subject: FW: Enhance and the decision today

Best regards,
Eric

-----Original Message-----
From: M.Gene Bond [mailto:mgbond@wfubmc.edu]
Sent: Monday, June 18, 2007 6:41 PM
To: ericdegroot; Petrauskas, Stanley; john.strony@spcorp.com
Subject: RE: Enhance and the decision today

You are correct! There is a draft manuscript, prepared by Philip Sager, that describes the Ultrasound Carotid IMT methods and replicate measurements at baseline. As you may remember, this manuscript was put on hold by SPRI because of Bo's concern about having 2 different baseline values (one for the baseline reproducibility study- and the second using efficacy data which were to be developed at the end of the study). Am trying to get a copy of the draft manuscript to distribute to the OC, and to all concerned.
Was not aware, that a team independent of the OC, was established by the SPONSORS to DEVELOP manuscripts associated with the ENHANCE study results.
What I do remember was an agreed upon decision by the OC (agreed upon by SP) was that this Committee would also serve as the Publications and Presentations Subcommittee for this study.
If the ENHANCE OC Committee has now been removed from this agreed upon procedure, I believe it important to document this change for the record, and to formally advise the Committee of this change and what there role is (or is not) relative to Publications and Presentations.

From: ericdegroot [mailto:ericdg@xs4all.nl]

From: Musliner, Thomas A.
Sent: Monday, July 09, 2007 11:19 PM
To: Stoner, Elizabeth; Morrison, Briggs W; Warner, Grey F
Cc: Stepanavage, Michael E.
Subject: FW: RE: ENHANCE -- CONFIDENTIAL

Importance: High
Sensitivity: Confidential

FYI -- John Strony sent me a copy of the email chain below, with Kastelein's heated reaction to the WWOC decision not to submit the placeholder abstract to AHA, plus John and Rick's responses.

Mike and I had a brief teleconference with John & Bo this afternoon, and they do not expect to have a further update on querying & missing data to discuss with us for at least several days. John said he would issue an email to the CDC explaining the delay in more detail (the "batch 3 issue" referred to below), and will also contact Diane Y with regard to earliest possible date for rescheduling the CDC ENHANCE teleconference.

Tom

-----Original Message-----
From: Strony, John [mailto:john.strony@spcorp.com]
Sent: Monday, July 09, 2007 5:14 PM
To: Musliner, Thomas A.
Subject: FW: RE: ENHANCE

-----Original Message-----
From: Veltri, Enrico
Sent: Monday, July 09, 2007 1:08 PM
To: 'J.J.P. Kastelein'
Cc: Strony, John
Subject: RE: RE: ENHANCE

John, we (collectively) have always stated that our intent was to present ENHANCE at AHA, but with the caveat that we needed quality and complete data. Both CEOs- Fred Hassan at SP, and Dick Clark at Merck- have gone on record publically to state that we would present ENHANCE results at a scientific forum later this year, BUT they have also stated that the quality of the data needs to be paramount to any presentation, and this call is left to me- and Liz Stoner, my counterpart at Merck. Liz and I met with you as you know earlier this year to convey this commitment, and there is much progress made, but as John outlined to you, we have some delays, yet I believe not insurmountable to still make a presentation at AHA. So these are the facts-

1) the carotid imaging, our primary endpoint, is not yet complete, we hope to have more information on the batch 3 issue this week. The blinded QCed imaging database did not get to us in time for a late-breaker abstract, and was so delayed, the WWOC meeting June 22nd did not feel confident of submitting an abstract without having the queeried database QC. Indeed SP received the final batch database late July 2nd, instead of the promised 1 week before late breaker deadline of June 29th. I do not see what you are raging about-- Editors, FDA etc, --the database is not QCed, not lock ready, and it remains blinded. So we are behaving in the highest scientific integrity, we want the data to be correct, whatever the result may be.

2) the femoral imaging is part of a key secondary endpoint, and not 'exploratory' and it should not be new to you that we decided to have

all imaging data locked. All those involved with the Operations calls-SP. Merck, outside consultants, CEL know that this is the case, we have been planning this, and indeed I gave the go-ahead to start the femoral readings 'at risk' July 2nd once we had received the carotid database in an effort to make a expeditious transition. As John mentioned, SP SOPs are clear on these database matters.

Thus, we must work together to complete the outstanding database cleanup and readings in a rigorous manner and not short cut for the sake of presentation. Having said that, even though we 'missed' the AHA late-breaker deadline, we have all been in the situation to attempt to get important scientific and clinical data on late-breaker sessions 'after' the formal deadlines. We must be more certain however that the data will be available however, and then we can work collectively to approach the scientific session chairs perhaps to get on the agenda.

I trust that you would be in agreement with a continuing effort to get quality and complete data for an AHA presentation, for I truly believe we will have very important results to share, and the trial and wait will have been worth it. The final chapter may well be a happy ending.

Hope you enjoy the rest of your vacation. Rick.

-----Original Message-----
From: J.J.P. Kastelein [mailto:J.J.Kastelein@amc.uva.nl]
Sent: Saturday, July 07, 2007 9:11 AM
To: Strony, John
Cc: Veltri, Enrico
Subject: Re: RE: ENHANCE

I have been travelling half the globe in the last 6 months to a number of large and important meetings at the strong wish of Merck to chair them or to present ezetimibe data. At every single one of them I was cleared to say that ENHANCE would be presented by me at AHA .

There is no reason whatsoever to include femorals; you will be seen as a company that tries to hide something and I will be perceived as being in bed with you !

John

----- Original Message -----
From: "Strony, John" <john.strony@spcorp.com>
Date: Friday, July 6, 2007 4:36 pm
Subject: RE: ENHANCE

> With regards to the below stated matter, I have been trying to call
> you including that of cell phone and office.
>
> It is true that the executive management of SP AND Merck through the
> auspices of the WWOC (World wide Operations Committee) have placed a
> hold on abstract submission. I immediately attempted to call your
> officebut there was no answer and no machine to leave a message. I
> also called your mobile and I successfully left a message for you to
> call leaving my
> cell phone number (which I always answer). After 36 hours and not
> hearing from you I sent you an e-mail.
>
> The decision to hold submission was based on several factors:
>
> 1)The primary data, namely that of the carotids, is undergoing the
> queryprocess. In parallel, the database has been migrated to a

> commerciallyavailable, validated system. We lost 3 weeks doing so. The

> data in the CEL was scattered throughout various computers and lap
> tops making
the
> process more complex than anticipated.
>
> 2) Collin and Jim are now auditing the image data base starting with
> batch 5 and working backwards. When they hit Batch 3 they identified
> 150 extraneous image values from that batch. The origin of these
> valuesare now being looked into. If the entry dates are after those in

> the current file then, by convention, the more recent entries are
> deemed valid. This would subject batch 3 to a potential re-query
> process. Thiscould cost several weeks. (As an aside, it was Batch 3
> that was the last
> batch accepted during the December crunch and it appears to
> contain a
> unique problem, namely 29% of the queries were answered by the
> replacement of image values with an unreadable code - the average is
> <3%). They have not audited batches 1, 2 or Vanguard, so brace
> yourself for potentially more issues.
>
> 3) Schering SOP's (the database resides in SP) forbid the locking and
> relocking of any database. A deviation requires signatures from the
> highest levels of management. Given the emphasis on compliance upper
> management decided not to take that risk which could in the eyes of a
> hard lined regulatory agency potentially invalidate the entire data
> base. We recognize that the Femoral and m-modes are exploratory
> but that
> makes no difference. (we have in our more recent trials made
> exploratoryimage analyses separate studies with unique databases
> thus avoiding such
> issues).
>
> 4) The timeline for the reading of the femorals alone has been a
> movingtarget. First it was 8 weeks, then 12, and then 16. This is
> under the assumption of having 4 readers. However, one of the four has

> failed qualification and now we are down to three. If all runs
> smoothly (whichhas never happened in ENHANCE) we are told it will take

> 17 weeks for the
> primary readings. Don't forget the querying process and clean-up
which
> is still not factored.
>
>
>
> I share your disappointment(s) and frustrations for this trial from
> hell. However, in the face of all this I have to say that we are
> proceeding in a positive direction; there is much confidence in the 2
> managers who are handling the operations and data base, and that
> in the
> end all involved in the trial could stand proud and say that the
> resultsare valid with no cause for second guessing.
>
> John
>
>
> -----Original Message-----
> From: J.J.P. Kastelein [mailto:J.J.Kastelein@amc.uva.nl]
> Sent: Friday, July 06, 2007 4:46 AM

> To: Strony, John
> Subject:
>
>
> Dear John ,
>
> is it correct that SP has decided not to present at AHA , but to await
>
> the two other , completely unvalidated , endpoints , which'analysis is
>
> going to take us straight into 2008 ??!!??
>
> If this is true , SP must have taken this decision without even the
> semblance of decency to consult me as PI of the study. I can tell
> you
> that if this is the case , our collaboration is over and I will
> take
> the appropriate steps to get in touch with the Editors of major
> Journals as well as with the FDA . This starts amelling like
> extending
> the publication for no other then political reasons and I cannot
> live
> with that .
>
> This is the second day of a long overdue holiday after a terrible
> year, thank you very much for yet another terrible chapter of this
> trial
>
> John
> **********
> This message and any attachments are solely for the
> intended recipient. If you are not the intended recipient, disclosure,
> copying, use or distribution of the information included in this
> message is prohibited -- Please immediately and permanently delete.

From: Veltri, Enrico [Enrico.Veltri@spcorp.com]
Sent: Tuesday, July 17, 2007 10:56 PM
To: J.J.P. Kastelein
Cc: Strony, John
Subject: RE: RE: ENHANCE

John, thank you for the note. I frankly understand the frustration, but this has been a long and painful process for all involved in this nightmare of a journey. The bottom line however is we all aspire to have quality and credible data, and results that we can stand behind-- whatever the 'truth'. I have been involved in over 20 clinical megatrials, with >200,000 patients enrolled, both positive and negative, stopping early for benefit and stopping early for harm, but I must say ENHANCE has been the most frustrating and, I likewise don't have a good sense of control of the process of data cleanup. You should be aware that the decision not to submit an abstract was a decision based on our concern (both Merck and Schering-Plough) that the quality, ie clean up, and the completed work received to date was not where it needed to be, and a high probability of indeed the withdrawal of the 'bland- no results' abstract, not something we wanted to do, ie yet again try to explain why we submitted then withdrew. In distinction, we would rather try to get it on the program later if and when we had greater confidence, this approach having been accomplished in the past, albeit not the usual path. John Strony did try to contact you but you were on vacation. Anyway, the issue at hand remains the quality of the data, we are analyzing the most recent submitted blinded database, and will be providing you our assessment and thoughts in the next few days. Best regards, Rick.

-----Original Message-----
From: J.J.P. Kastelein [mailto:j.j.kastelein@amc.uva.nl]
Sent: Friday, July 13, 2007 8:12 AM
To: Veltri, Enrico
Cc: Strony, John
Subject: RE: RE: ENHANCE

Dear Rick,

I am glad you took the trouble of providing me with such a long answer.

The raging part of my former emails coms from an enormous amount of frustration and a feeling that I have no control whatsoever on anything that relates to ENHANCE. As you know, in my normal state of mind, I am a controlled individual and I am not hard to work with.
However, in all my previous experiences as a member of a Steering Committee or as a PI, I felt I was in control. With ENHANCE, that is totally the opposit.
The database is at SP, consultants like Gene Bond are in my opinion impossible to work with and never agree with me, Bo Yang has made several crucial mistakes on the way that costs us 9 monts, Eric is a nightmare to work with in terms of organization and I can go on and on.
The last example of this "never working with me" is the fact that you have decided to withdrawn the abstract. This is not necessary. You could have send in an empty abstract that as my friend at AHA tell me can be filled with data one week before AHA itself and if you were too late, you simply withdraw it. One phonecall to me would have cleared all of this. This is exactly what I have done with Pfizer for the Torcetrapib latebreakers at ACC this year. The data were ready 3 days before ACC.

Also, I am constantly under pressure from Merck to plan all sorts of activities, before, at and after AHA. Because I !!! will be the one who have to stand up and present and defend the data, and I would deeply appreciate being involved again and not just simply at the end of a long decision line.

Regards, John

****
John J.P. Kastelein, MD, PhD
Professor of Medicine
Chairman, Dept. of Vascular Medicine
Academic Medical Center
Meibergdreef 9, Room F4-159.2
1105 AZ Amsterdam, The Netherlands
tel: +31 20 566 6612
fax: +31 20 566 9343
email: j.j.kastelein@amc.uva.nl

-----Oorspronkelijk bericht-----
Van: Veltri, Enrico [mailto:Enrico.Veltri@spcorp.com]
Verzonden: maandag 9 juli 2007 19:08
Aan: J.J.P. Kastelein
CC: Strony, John
Onderwerp: RE: RE: ENHANCE

John, we (collectively) have always stated that our intent was to present ENHANCE at AHA, but with the caveat that we needed quality and complete data. Both CEOs- Fred Hassan at SP, and Dick Clark at Merck- have gone on record publically to state that we would present ENHANCE results at a scientific forum later this year, BUT they have also stated that the quality of the data needs to be paramount to any presentation, and this call is left to me- and Liz Stoner, my counterpart at Merck. Liz and I met with you as you know earlier this year to convey this commitment, and there is much progress made, but as John outlined to you, we have some delays, yet I believe not insurmountable to still make a presentation at AHA. So these are the facts-

1) the carotid imaging, our primary endpoint, is not yet complete, we hope to have more information on the batch 3 issue this week. The blinded QCed imaging database did not get to us in time for a late-breaker abstract, and was so delayed, the WWOC meeting June 22nd did not feel confident of submitting an abstract without having the queeried database QC. Indeed SP received the final batch database late July 2nd, instead of the promised 1 week before late breaker deadline of June 29th. I do not see what you are raging about-- Editors, FDA etc, --the database is not QCed, not lock ready, and it remains blinded. So we are behaving in the highest scientific integrity, we want the data to be correct, whatever the result may be.

2) the femoral imaging is part of a key secondary endpoint, and not 'exploratory' and it should not be new to you that we decided to have all imaging data locked. All those involved with the Operations calls- SP. Merck, outside consultants, CEL know that this is the case, we have been planning this, and indeed I gave the go-ahead to start the femoral readings 'at risk' July 2nd once we had received the carotid database in an effort to make a expeditious transition. As John mentioned, SP SOPs are clear on these database matters.

Thus, we must work together to complete the outstanding database cleanup and readings in a rigorous manner and not short cut for the sake of presentation. Having said that, even though we 'missed' the AHA late-breaker deadline, we have all been in the situation to attempt to get important scientific and clinical data on late-breaker sessions 'after' the formal deadlines. We must be more certain however that the data will be available however, and then we can work collectively to approach the scientific session chairs perhaps to get on the agenda.

From: Musliner, Thomas A.
Sent: Wednesday, August 08, 2007 8:46 PM
To: Morrison, Briggs W
Cc: Stoner, Elizabeth
Subject: RE: Can either of you join?
Eastham -- the gods willing

Am really nervous about entrusting S-P alone on this. Based on Kastelein's prior comments, we're at risk of being put in very bad light by a very key opinion leader. From the position Rick expressed at the last CDC, I have no confidence he would go in with a willingness to compromise his expressed view on how this should go. Have you gotten any feedback that Rick has softened on the position that re-read is necessary no matter what the independent consultants recommend?

Tom

From: Morrison, Briggs W
Sent: Wednesday, August 08, 2007 3:27 PM
To: Musliner, Thomas A.; Stoner, Elizabeth
Subject: RE: Can either of you join?

I am on vacation.
On Cape Cod! (We are in west falmouth, where are you?)
We may have to entrust them on this one...
briggs

From: Musliner, Thomas A.
Sent: Wednesday, August 08, 2007 3:26 PM
To: Morrison, Briggs W; Stoner, Elizabeth
Subject: RE: Can either of you join?
Importance: High

Unfortunately this falls right in the middle of my pre-planned vacation in Cape Cod. But I think its essential that someone from Merck be present. I gather you're on vacation as well, Briggs. Might Liz be available???

Tom

From: Morrison, Briggs W
Sent: Wednesday, August 08, 2007 3:12 PM
To: Stoner, Elizabeth; Musliner, Thomas A.
Subject: Can either of you join?

From: Veltri, Enrico [mailto:Enrico.Veltri@spcorp.com]
Sent: Wednesday, August 08, 2007 1:39 PM
To: Warner, Grey F; Mcnicholas, Sean
Cc: Christiansen, Soren Bo (WS); Russo, Ray; Morrison, Briggs W; Strony, John; Yang, Bo; Suresh, Ramachandran; Stoner, Elizabeth
Subject: RE:

Due to vacation schedules and conflicts for key participants, the earliest date secured to meet with John Kastelein will be Monday August 20th in Amsterdam.

Briggs, will you, Liz, or Tom accompany John, Bo, Ram and me? I would like to keep this to a small group. Rick.

From: Stoner, Elizabeth
Sent: Tuesday, August 21, 2007 1:24 AM
To: Morrison, Briggs W; Musliner, Thomas A.
Cc: Pasternak, Richard; Korn, Scott H.; Kim, Peter S; Christiansen, Soren Bo (WS); Khanna, Deepak K; Warner, Grey F; Tershakovec, Andrew M.
Subject: RE: Thank you

Wanted to provide you all with my perspective of the meeting this am with Kastelein,

The meeting was cordial and we had a good productive, and open discussion. I do not have electronic copies of the slide set, but very similar to what we had discussed at CDC.
Ram led most of the discussion, and Kastelein was indeed convinced that at least for the subset of patients with biologically-implausible (but likely image-faulty) data points that we needed a clear pre-defined pathway forward to get us to results and presentation ASAP.

John Kastelein reiterated several times during the conversation his strong concern that he is losing credibility by the long delay in presenting the ENHANCE data.
We agreed that we would convene a pane of experts,including Michael Bots,and an American expert, and regulatory expertise (probably David orloff)…Hopefully in the first 2 weeks of September to come up with an agreed upon path forward, which we would respect and then execute. I asked Sp to prepare a detailed background package to provide to the consultants in preparation for the meeting.
A likely next step will be some "adjudication", although we could not agree at this meeting as to whether it would be in a subset of patients, or for the entire cohort,…This will clearly be a topic for discussion with the Expert Panel.
We also discussed as to whether AHA-)07 was out of the question, and in my opinion it is not, if we can get SP to schedule these meetings and move quickly.
John Kastelein feels strongly that the carotids are not required, but this became a moot point, as they are currently being read, and are not on the critical path. I asked SP to begin to quality review fo the femorals,so that we could clean the data in parallel.

Hope this is helpful. I would be happy to answer any additional questions.
Liz

From: Morrison, Briggs W
Sent: Saturday, August 18, 2007 10:41 AM
To: Stoner, Elizabeth
Subject: Thank you

Hi Liz
Thanks for your help here.
I am including the background package we sent to Peter Kim. This may come up during your time with Rick and SP. Our position is clear and consistent with what you (the CDC) decided in the spring -- lets look at the enrollment and rates and decide again in the fall. And since Gene pushed hard again -- after the Aug CDC -- to not remove STEMIs, we again revisited the data. We reviewed with Barry and Peter H and all are in agreement that we currently see no scientific justification for Rick's position. We anticipate Peter K and Tom K will have to resolve. If Rick has additional data for us to consider, we welcome the dialogue.
Have a safe trip.
Can you let me know about the call on Monday -- after the meeting? I'd like to join, if possible.
Thanks again,
Briggs << Message: RE: Does this timeline work for you? >>

From: Stoner, Elizabeth
Sent: Saturday, August 18, 2007 8:32 AM
To: Christiansen, Soren Bo (WS); Warner, Grey F; Morrison, Briggs W; Musliner, Thomas A.
Subject: FW: ENHANCE

Just FYI….

From: Stoner, Elizabeth
Sent: Saturday, August 18, 2007 8:25 AM
To: 'j.j.kastelein@amc.uva.nl'
Subject: RE: ENHANCE

Dear Dr. Kastelein,

From: Strony, John
Sent: Tuesday, August 22, 2006 2:41 PM
To: Bransford, Toni; Veltri, Enrico
Subject: FW: ENHANCE

Importance: High
A bombshell from John K.

-----Original Message-----
From: J.J.P. Kastelein [mailto:j.j.kastelein@amc.uva.nl]
Sent: Tuesday, August 22, 2006 6:26 AM
To: Strony, John
Cc: Mieke Trip; ericdg@xs4all.nl; Onno Bakker
Subject: ENHANCE
Importance: High

Dear John,

This is a terribly important email.

As things are currently understood by me, we have the following realities to deal with:

1) We have to analyse 870 datasets (patients)

2) SP has decided not to use Mark Klinkenbijl as reader and therefor, we have 4 readers.

3) We received the first datasets this morning, actually the 22nd of August.

4) In the VANGUARD study, our readers managed to finish 15 datasets per week which equals 40 - 45 hours of reading. This is utterly impossible to keep up for more than a few weeks. People will start making mistakes and can't physically cope with this. The maximum number of datasets per week for a single reader is 10.

All of the above means that we will not even be ready by Christmas of this year!!!!!

The only possibility of meeting the ACC deadline is

1) To allow Mark Klinkenbijl to participate in the reading after some severe additional training by Eric de Groot.

2) To certify at an incredible speed two additional readers

Furthermore, if Mark would be allowed to act as the 5th reader, the data from the VANGUARD study could be incorporated into the final analyses which would save 100 datasets!

We need to talk as soon as you get up.

From: Veltri, Enrico [Enrico.Veltri@spcorp.com]
Sent: Monday, September 17, 2007 8:48 PM
To: Mcnicholas, Sean; Strony, John
Subject: RE: ENHANCE - status

Soren is a prick. How's that for staying calm. Tell him to f' off. Rick.

-----Original Message-----
From: Mcnicholas, Sean
Sent: Friday, September 14, 2007 4:51 PM
To: Strony, John; Veltri, Enrico
Subject: FW: ENHANCE - status

Comments ..... And please stay calm and reply back only to me Sean

Sent by GoodLink (www.good.com)

-----Original Message-----
From: Christiansen, Soren Bo (WS)
[mailto:soren_christiansen@merck.com]
Sent: Friday, September 14, 2007 04:48 PM Eastern Standard Time
To: Allibone, Kathleen M; Hill, Barbara; Bastos, Jose A.; Strigini, Bruno; Christiansen, Soren Bo (WS); Granata, Francesco; Helfer, Gerda; Petitti, Joanne; Mendoza, Miriam; Jones, Monica; Oschmann, Stefan; Mcnicholas, Sean; Silva, Ariane D.; Warner, Grey F
Subject: ENHANCE - status

To the Board : I have to express my concern over how SPRI is interacting with one of the most important customers in EMEA. During the meeting at Dr. Kasteleins Hospital it was agreed to conduct a meeting with outside Consultants by mid September. According to email below there has been no communication to Dr. Kastelein with respect to when the meeting will take place. This raises a question, in my mind : is this high enough on the SPRI priority list ? Thanks Soren

---

From: J.J.P. Kastelein [mailto:j.j.kastelein@amc.uva.nl]
Sent: Friday, September 14, 2007 3:05 AM
To: Christiansen, Soren Bo (WS)
Cc: O'Malley, Justine; Nouss, Edgar M.
Subject: RE: ENHANCE Stand by - revised

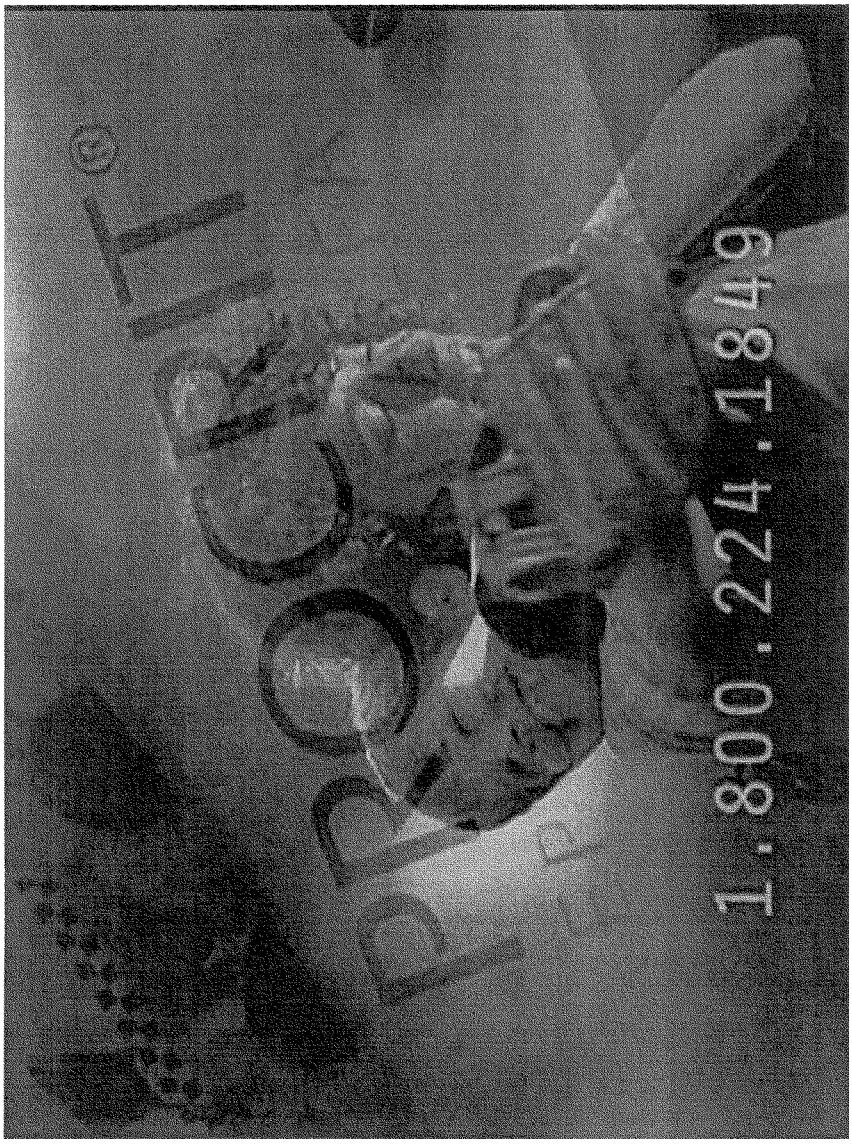
Dear Soren,

Thanks for the changed statement. I have no further questions.

I have heard nothing about the Consultant Meeting. I will write Strony and Veltri right now.

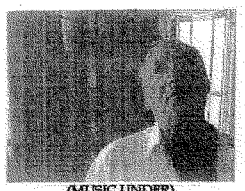
Regards, John

****
John J.P. Kastelein, MD, PhD
Professor of Medicine
Chairman, Dept. of Vascular Medicine
Academic Medical Center
Meibergdreef 9, Room F4-159.2

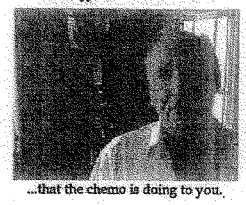

1.800.224.1849

ORTHO BIOTECH
PROCRIT

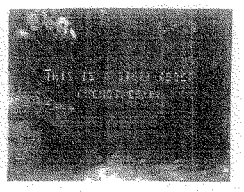
"FROM THE HEART"
TV :60 JJOP-6802 PAGE 1

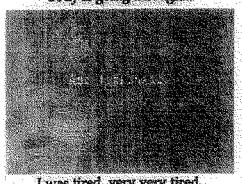


(MUSIC UNDER)
MAN: There are certain things your body is going through...



...that the chemo is doing to you.





I was tired, very very tired.



One time, my grandchildren were all over...



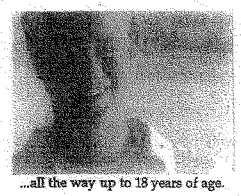
...and they all went out and got ice cream....



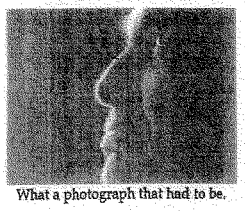
...and they're all lined up on the porch...all with ice cream.



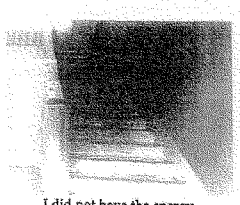
They start from the age of 3...



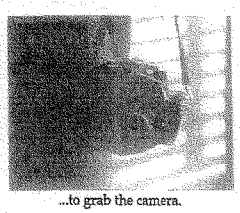
...all the way up to 18 years of age.



What a photograph that had to be.



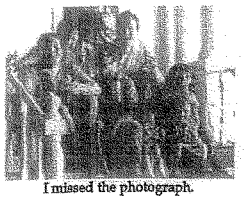
I did not have the energy to go upstairs...



...to grab the camera.

ORTHO BIOTECH
PROCRIT

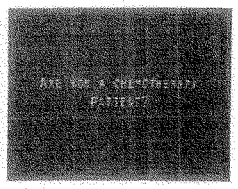
"FROM THE HEART"
TV :60 JJOP-6802 PAGE 2

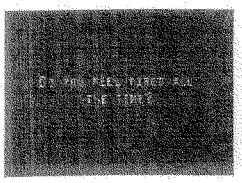


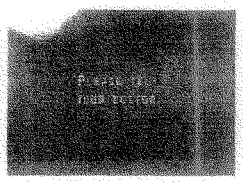
I missed the photograph.

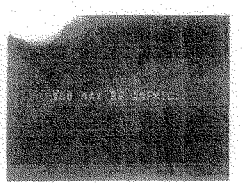


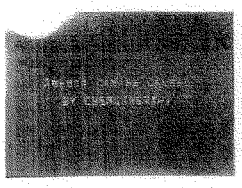
To me, a once in a lifetime opportunity.

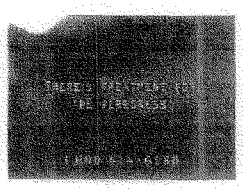


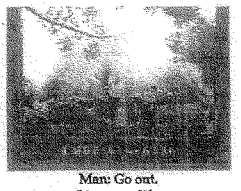




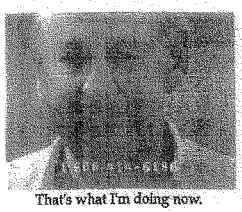




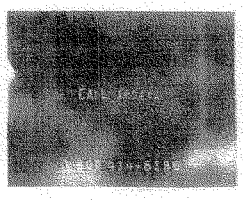


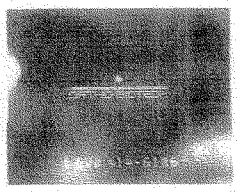


Man: Go out.
Live your life.



That's what I'm doing now.





ORTHO BIOTECH
PROCRIT

"ANTHEM"
TV :60 PAGE 1

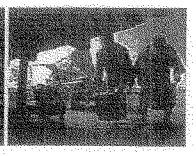


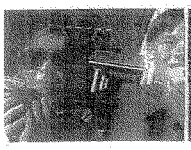
(MUSIC UNDER)
WOMAN 1: Today I made an omelete.



MAN 1: I picked an apple.







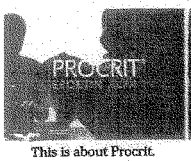
WOMAN 2: I sent a fax.



ANNCR: This is about chemotherapy...



...and living your life.



This is about Procrit.



If you're a chemotherapy patient and you feel tired and weak...



...ask your doctor about Procrit.



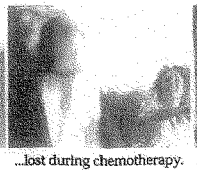
WOMAN 3: I played a game.



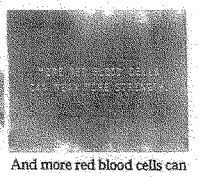
ANNCR: Procrit is a natural way...



...to regain red blood cells...



...lost during chemotherapy.



And more red blood cells can mean more strength.

ORTHO BIOTECH
PROCRIT

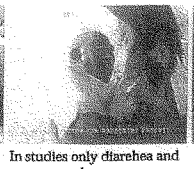
"ANTHEM"
TV :60 PAGE 2



MAN 2: I caught a fish!



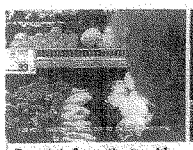
ANNCR: Procrit is safe and effective.



In studies only diarrhea and edema...



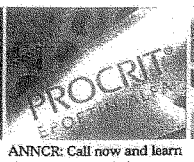
...occurred more often with Procrit than placebo.



Procrit is for patients with non-myloid cancers.



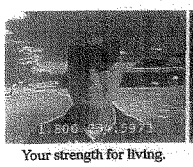
WOMAN 4: I went to the store.



ANNCR: Call now and learn how Procrit can help you...



...get back the strength you need.





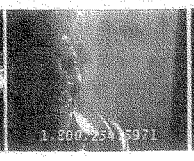




Your strength for living.

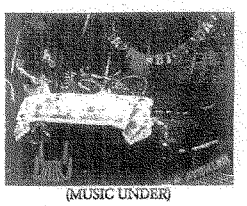


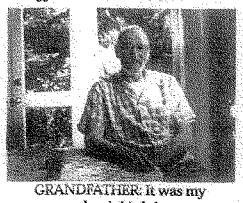


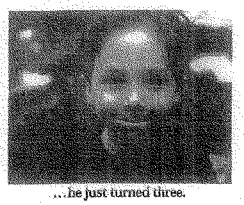




ORTHO BIOTECH PRODUCTS, L.P.
PROCRIT
"BIG BOY BED" TV :60
JJOP-6101 PAGE 1

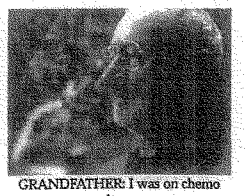

(MUSIC UNDER)

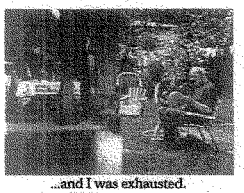

GRANDFATHER: It was my grandson's birthday....


...he just turned three.

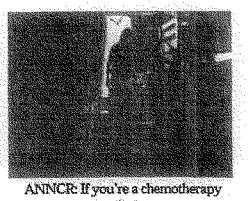

GRANDFATHER: We were going to move him out of his crib,...

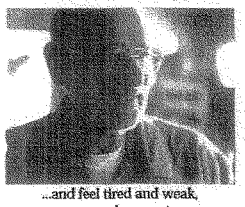

...and buy him a big boy bed.

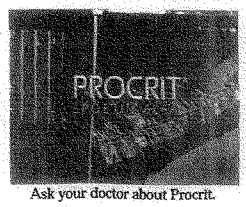

GRANDFATHER: I was on chemo then...


...and I was exhausted.
GRANDSON: Grandpa.


GRANDFATER: I said to the doctor, I need help. I'm on a mission.

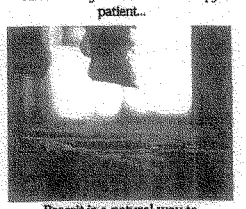

ANNCR: If you're a chemotherapy patient...


...and feel tired and weak, you may be anemic.

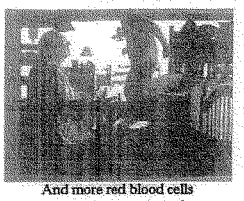


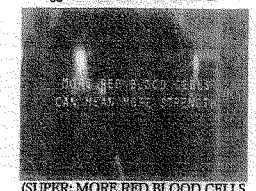
Ask your doctor about Procrit.

(SUPER: PROCRIT® EPOETIN ALFA)


Procrit is a natural way to regain red blood cells lost during chemotherapy.

ORTHO BIOTECH PRODUCTS, L.P.
PROCRIT
"BIG BOY BED" TV :60
JJOP-6101 PAGE 2


And more red blood cells
can mean more strength.

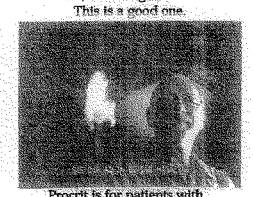


(SUPER: MORE RED BLOOD CELLS
CAN MEAN MORE STRENGTH.)

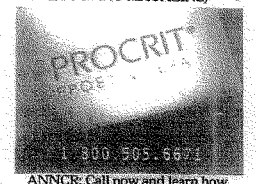

GRANDFATHER:
Oh, this is a great one.
This is a good one.


ANNCR: Procrit is proven and safe.
In studies, only diarrhea and edema...
(SUPER: BY PRESCRIPTION ONLY)


...occurred more often with Procrit
than placebo. (SUPER: SEE OUR AD
IN COPING MAGAZINE)


Procrit is for patients with
non-myeloid cancers.
(SUPER: SEE OUR AD IN COPING MAGAZINE)


GRANDFATHER: How do you like
it up here now?
GRANDSON: Good.



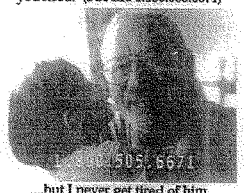
ANNCR: Call now and learn how
Procrit can help you get back the strength
you need. (SUPER: 1.800.505.6671)



GRANDFATHER: See, what'd I tell
ya? ANNCR: Your strength for living.
(SUPER: 1.800.505.6671)



GRANDFATHER: He takes
a lot of energy...
(SUPER: 1.800.505.6671)



...but I never get tired of him.
(SUPER: 1.800.505.6671)



(SUPER: PROCRIT®
EPOETIN ALFA
STRENGTH FOR LIVING®
WWW.PROCRIT.COM
1.800.505.6671)

vms

PRODUCT Procrit
MARKET Network
PROGRAM Today
CODE # 020607171
TITLE Shopping At Sal's Market

LENGTH 60
STATION WNBC
DATE 06/25/2002
TIME 07:52 AM



(MUSIC IN)



MRS. PANTINI: I like to shop every day. 8 AM sharp, Sal's Fruit Market.



oh, he's got the best tomatoes in town.



MRS. PANTINI: When I started chemo, my doctor said that I might become anemic. It made me feel weak. I never expected to be too tired to make it to Sal's.



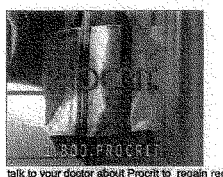
The day he had to deliver my order was one of the saddest days of my life. Thank you Sal.



I asked my doctor about Procrit. MALE ANNCR: Procrit is for chemotherapy-related anemia and patients with most kinds of cancer.



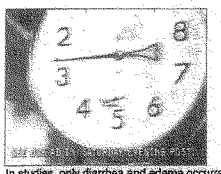
If you're on chemotherapy and too tired to do the things you used to do,



talk to your doctor about Procrit to regain red blood cells and more red blood cells can mean more strength. (GRFX: MORE RED BLOOD CELLS CAN MEAN MORE STRENGTH)



SAL: Welcome back, Mrs. Pantini. ANNCR: Procrit is proven and safe.



In studies, only diarrhea and edema occurred more often with Procrit than placebo. Call now and learn how Procrit can help you get back the strength you need. (GRFX: EPOETIN ALFA)



your strength for living. MRS. PANTINI: Buying fresh takes a little more energy.



I wouldn't have it any other way. (MUSIC OUT)

ALSO AVAILABLE ON VIDEO CASSETTE

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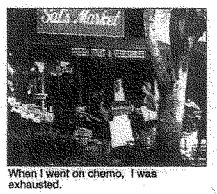
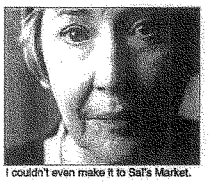
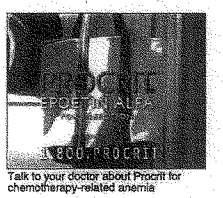
PRODUCT	Procrit	**LENGTH**	30
MARKET	Network	**STATION**	ABC
PROGRAM	Drew Carey Show	**DATE**	06/26/2002
CODE #	020608071	**TIME**	09:29 PM
TITLE	Shopping At Sal's Market	**REV OF #**	020607171


(MUSIC IN) MRS. PANTINI: I like to shop every day.

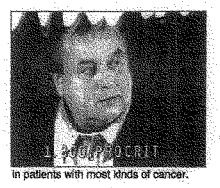

When I went on chemo, I was exhausted.


I couldn't even make it to Sal's Market.

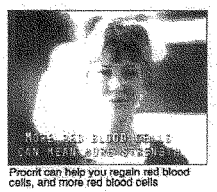

MALE ANNCR: If you're on chemotherapy and feel tired, you may be anemic.



Talk to your doctor about Procrit for chemotherapy-related anemia

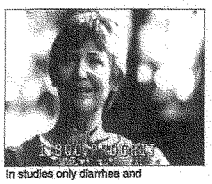


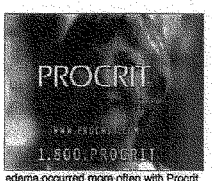
in patients with most kinds of cancer.


Procrit can help you regain red blood cells, and more red blood cells


can mean more strength. SAL: Welcome back, Mrs. Pantini.


ANNCR: Procrit is proven and safe.


In studies only diarrhea and



edema occurred more often with Procrit than placebo.


MRS. PANTINI: Buying fresh takes a little more energy, but I love it. (MUSIC OUT)

ALSO AVAILABLE ON VIDEO CASSETTE

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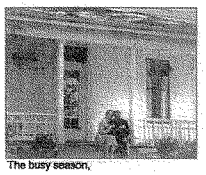
PRODUCT	Procrit	**LENGTH**	60
MARKET	Network	**STATION**	NBC
PROGRAM	Today	**DATE**	06/02/2003
CODE #	030600087	**TIME**	08:14 AM
TITLE	He Dreamed Of Running A Bed & Breakfast		



(MUSIC IN) MAN: It's always been our dream to run a bed and breakfast.



The busy season,



it's only three months long, but we gear up for it every year. Then I had to go on chemo. Doctor said I might become anemic, maybe feel weak.



But it just drained me. The day we talked about cancer...guests– WOMAN: Maybe we should cancel the Nealsons.



MAN: They've been coming for years. I had to do something, so I asked my doctor about Procrit.



MALE ANNCR: Procrit is for chemotherapy-related anemia in patients with most kinds of cancer. If you're on chemo



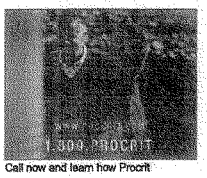
and too tired to do the things you used to do, talk to your doctor about Procrit. Procrit helps rebuild red blood cells



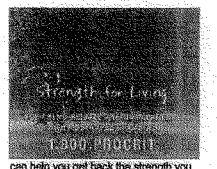
and more red blood cells can mean more strength. WOMAN: Here come the Nealsons. MAN: I'm ready. ANNCR: Procrit is proven



and safe. In studies only diarrhea and edema occurred more often with Procrit than placebo.



Call now and learn how Procrit



can help you get back the strength you need. Your strength for living. MAN: Around here,



there's no slowing down. (MUSIC OUT)

VIDEO ALSO AVAILABLE

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PRODUCT	Procrit	**LENGTH**	30
MARKET	Network	**STATION**	ABC
PROGRAM	One Life To Live	**DATE**	06/04/2003
CODE #	030600656	**TIME**	02:57 PM
TITLE	He Dreamed Of Running A Bed & Breakfast	**REV OF #**	030600087



(MUSIC IN)



MAN: It's always been our dream to run a bed and breakfast.



Then I had to go on chemo, and it just drained me.



MALE ANNCR: If you're on chemo and feel tired, you may be anemic.



MAN (VO): We even talked about canceling our guests.



ANNCR: Talk to your doctor about Procrit.



For chemotherapy-related anemia, in patients with most kinds of cancer. (GRFX: FOR INJECTION)



Procrit helps rebuild red blood cells



and more red blood cells can mean more strength.



MAN/WOMAN: Here come the Nielsens.



ANNCR: Procrit is proven and safe. In studies, only diarrhea and edema occurred more often with Procrit than placebo. SUPER: FOR CHEMO-RELATED ANEMIA IN PATIENTS WITH MOST TYPES OF CANCER



MAN: Hear that? No slowing down. (MUSIC OUT)

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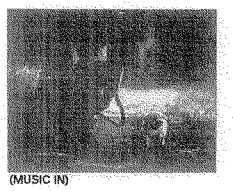
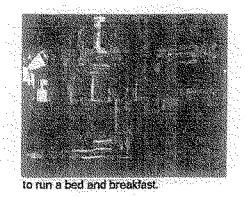
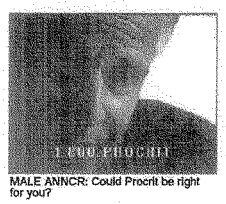
PRODUCT	Procrit	LENGTH	15
MARKET	New York, NY	STATION	WCBS
PROGRAM	Guiding Light	DATE	07/09/2003
CODE #	030701527	TIME	10:59 AM
TITLE	He Dreamed Of Running A Bed & Breakfast	REV OF #	030600087


(MUSIC IN)


MALE (VO): It's always been our dream


to run a bed and breakfast.



MALE ANNCR: Could Procrit be right for you?



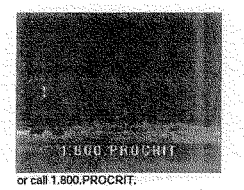
(MUSIC)



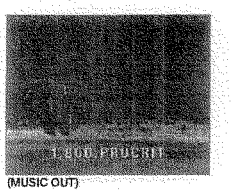
Talk to your doctor



about Procrit



or call 1.800.PROCRIT.



(MUSIC OUT)

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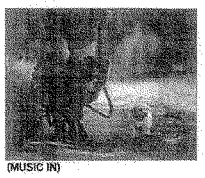
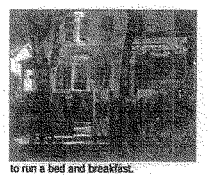
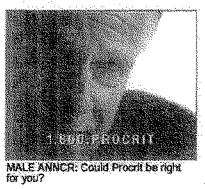
PRODUCT	Procrit	LENGTH	15
MARKET	New York, NY	STATION	WCBS
PROGRAM	Guiding Light	DATE	07/09/2003
CODE #	030701527	TIME	10:59 AM
TITLE	He Dreamed Of Running A Bed & Breakfast	REV OF #	030600087


(MUSIC IN)


MALE (VO): it's always been our dream


to run a bed and breakfast.



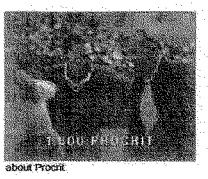
MALE ANNCR: Could Procrit be right for you?



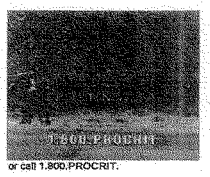
(MUSIC)



Talk to your doctor



about Procrit



or call 1.800.PROCRIT.



(MUSIC OUT)

VIDEO ALSO AVAILABLE

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PRODUCT	Procrit	LENGTH	60
MARKET	New York, NY	STATION	MSNBC
PROGRAM	The Abrams Report	DATE	08/05/2003
CODE #	030800539	TIME	09:27 PM
TITLE	Dreamed Of Running A Bed/Pamphlets Shown	REV OF #	030600087



(MUSIC IN) MAN: It's always been our dream to run a bed and breakfast.



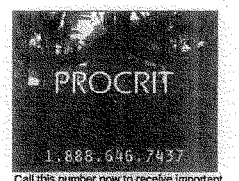
Then I had to go on chemo. Doctors said I might become anemic, maybe feel weak,



but it just drained me. We even talked about canceling our guests. I had to do something.



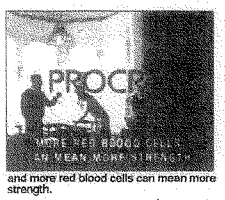
MALE ANNCR: Are you or someone you love about to start chemotherapy?



Call this number now to receive important information about Procrit. Procrit is for chemotherapy related anemia in patients with most kinds of cancer.



Procrit helps rebuild red blood cells lost during chemotherapy,



and more red blood cells can mean more strength.



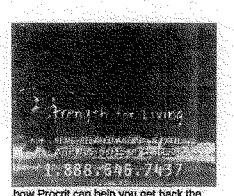
Call now for helpful information on how to manage chemo side effects and how to find out if you could be anemic.



WOMAN: Here come the Nielsons. MAN: I'm ready. ANNCR: Procrit is proven and safe. In studies, only diarrhea and edema



occurred more often with Procrit than placebo. So, talk to your doctor, call now and learn



how Procrit can help you get back the strength you need. Your strength for living.



MAN: Around here, there's no slowing down. (MUSIC OUT)

ALSO AVAILABLE ON VIDEO CASSETTE

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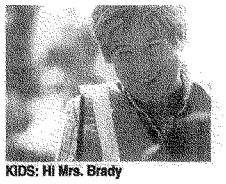
Anderson DDB Health & Lifestyle

PRODUCT PROCRIT

CODE# JJNO6433
LENGTH :60
TITLE Crossing Guard DRTV



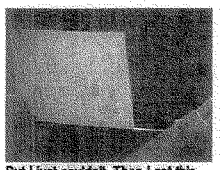
MRS. BRADY: For years the kids have called me their guardian angel.



KIDS: Hi Mrs. Brady



MRS. BRADY: When I got cancer and the chemo made me anemic and weak, I tried to keep working.



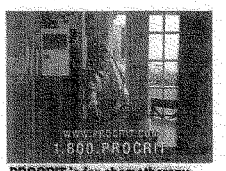
But I just couldn't. Then I got this card. 'Come back soon.'



I had to do something.



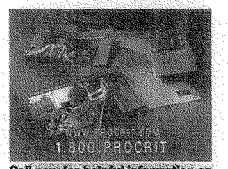
VO: If you or someone you love is on chemo, call this number now to receive important information about PROCRIT.



PROCRIT is for chemotherapy-related anemia in patients with most kinds of cancer.



PROCRIT is proven to help rebuild red blood cells, which can mean more strength.



Call now for helpful information on how to manage chemo side effects, and how to find out if you could be anemic.



KIDS: Hi Mrs. Brady!

PROCRIT is not for patients with uncontrolled high blood pressure, and may increase the risk of blood clots. Ask your doctor if PROCRIT is right for you.



Call now and learn how PROCRIT can help you get back the strength you need.

Your strength for living.



MRS. BRADY: I'm back, and there's no stopping me.

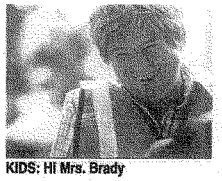
Anderson DDB Health & Lifestyle

PRODUCT PROCRIT

CODE# JJNC3403
LENGTH :30
TITLE Crossing Guard - Tech Rev



MRS. BRADY: For years, the kids have called me their guardian angel.



KIDS: Hi Mrs. Brady



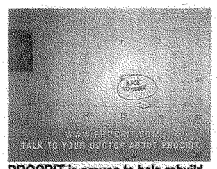
When I got cancer the chemo made me anemic...and too weak to keep working.



I had to do something. I asked my doctor about PROCRIT.



V.O.: PROCRIT is for chemotherapy-related anemia in patients with most kinds of cancer.



PROCRIT is proven to help rebuild red blood cells...



...which can mean more strength.



Ask your doctor if PROCRIT is right for you.



PROCRIT is not for patients with uncontrolled high blood pressure, and may increase the risk of blood clots.



MRS. BRADY: I'm back, and there's no stopping me.

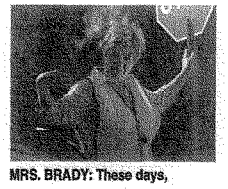
Anderson DDB Health & Lifestyle

PRODUCT PROCRIT

CODE# JJNO 5401
LENGTH :15
TITLE Crossing Guard



(Music in)



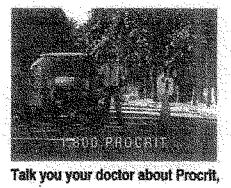
MRS. BRADY: These days,



I welcome the morning rush.



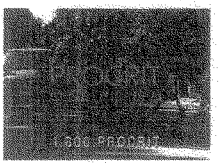
VO: Could Procrit be right for you?



Talk you your doctor about Procrit,



or call



1.800.PROCRIT.

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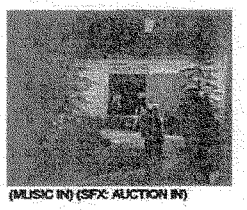
PRODUCT	Procrit	LENGTH	60
MARKET	New York, NY	STATION	WNYW
PROGRAM	News	DATE	04/04/2005
CODE #	050400268	TIME	05:23 AM
TITLE	Charlie The Auctioneer/Ladies Home Journal	REV OF #	021207236



(MUSIC IN) (SFX: AUCTION IN)



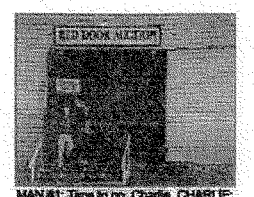
CHARLIE: I've always talked fast and loved antiques. Then I got sick and had to go on chemo.



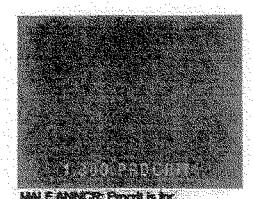
Doctor told me I might become anemic. Made me feel weak, but it slowed



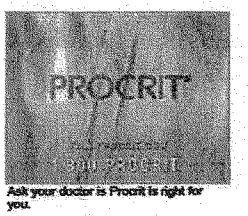
me right down. For the first time in 30 years, I was too tired to work. (SFX: OUT)



MAN #1: Time to go, Charlie. CHARLIE: I had to get my strength back. I asked my doctor about Procrit.



MALE ANNCR: Procrit is for chemotherapy-related anemia in patients with most kinds of cancer.



Ask your doctor is Procrit is right for you.



Procrit is proven to help rebuilt red blood cells, which can mean more strength. MALE (VO): Good to see ya.

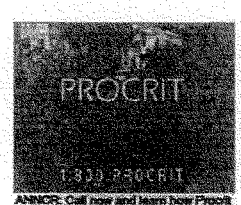


MAN #2: It's good to see you, Charlie. CHARLIE: Good to be back.

SUPER: BY PRESCRIPTION ONLY. SEE OUR AD IN "LADIES HOME JOURNAL."



ANNCR: Procrit is not for patients with uncontrolled high blood pressure and may increase the risk of blood clots. CHARLIE: Okay, folks. Let's go. (SFX: AUCTION IN)



ANNCR: Call now and learn how Procrit can help you get back the strength you need, your strength for living. (SFX: OUT)

SUPER: WWW.PROCRIT.COM



CHARLIE: Yeah, I got two speeds. Fast and faster. (MUSIC OUT)

SUPER: FOR CHEMO-RELATED ANEMIA IN PATIENTS WITH MOST TYPES OF CANCER.

VIDEO ALSO AVAILABLE IN ANALOG & DIGITAL FORMATS

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330 West 42nd Street, New York, NY 10036 T 212.736.2910

Anderson DDB Health & Lifestyle

MSI-961

PRODUCT PROCRIT

CODE# JJNO6523
LENGTH :60
TITLE "Auctioneer" 2005



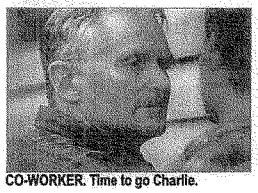
CHARLIE:
I've always talked fast and loved antiques.



CHARLIE VO: Then I got sick and had to go on chemo. The doctor told me I might become anemic,maybe feel weak...but it slowed me right down.



CHARLIE:
For the first time in 30 years, I was too tired to work.



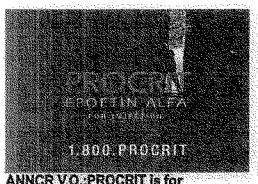
CO-WORKER. Time to go Charlie.



CHARLIE V.O.:
I had to get my strength back.



CHARLIE:
I asked my doctor about PROCRIT.



ANNCR V.O.:PROCRIT is for chemotherapy-related anemia in patients with most kinds of cancer..



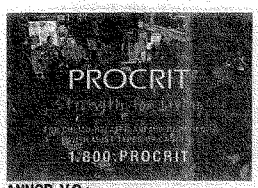
ANNCR V.O.:PROCRIT is proven to help rebuild red blood cells... which can mean more strength.



ANNCR. V.O.: PROCRIT is not for patients with uncontrolled high blood pressure, and may increase the risk of blood clots.



CHARLIE: Okay folks, let's go! (Auctioneering dialogue under)



ANNCR. V.O.:
Call now and learn how PROCRIT can help you get back the strength you need... your strength for living..



CHARLIE:
Yep, I've got two speeds – fast and faster.

vms

PRODUCT Procrit
MARKET Network
PROGRAM Imus In The Morning
CODE # 050511806
TITLE Charlie The Auctioneer/Ladies' Home.

LENGTH 30
STATION MSNBC
DATE 05/31/2005
TIME 06:50 AM
REV OF # 021207236



(MUSIC IN) CHARLIE: I've always talked fast.



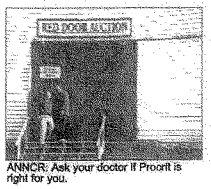
(SFX: CHARLIE AUCTIONEERING IN & OUT)



but the chemo slowed me right down. For the first time ever, I was too tired to work.



(SFX: DOOR CLOSING IN & OUT) MALE ANNCR: If you're on chemo and feel tired, you may be anemic. MAN: Time to go, Charlie.



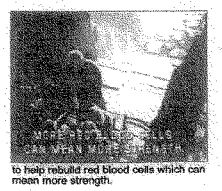
ANNCR: Ask your doctor if Procrit is right for you.



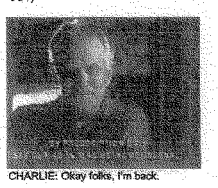
Procrit is for chemotherapy-related anemia in patients with most kinds of cancer. (SFX: DOOR OPENING IN & OUT)



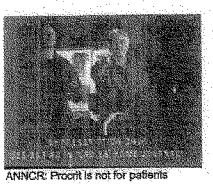
Procrit is proven



to help rebuild red blood cells which can mean more strength.



CHARLIE: Okay folks, I'm back.



ANNCR: Procrit is not for patients



with uncontrolled high blood pressure and may increase the risk of blood clots. (SFX: CHARLIE AUCTIONEERING IN & OUT)

SUPER: FOR CHEMO-RELATED ANEMIA IN PATIENTS WITH MOST TYPES OF CANCER

SUPER: BY PRESCRIPTION ONLY. SEE OUR AD IN "LADIES' HOME JOURNAL."



CHARLIE: In this business, you've gotta be fast. (MUSIC OUT)

VIDEO ALSO AVAILABLE IN ANALOG & DIGITAL FORMATS

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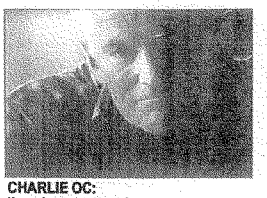
Anderson DDB Health & Lifestyle

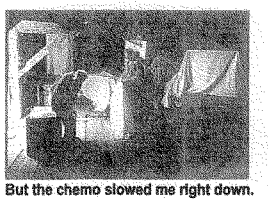
MSI-960

PRODUCT PROCRIT

CODE# JJNO 3510
LENGTH :30
TITLE "Auctioneer" Rev



CHARLIE OC:
I've always talked fast.



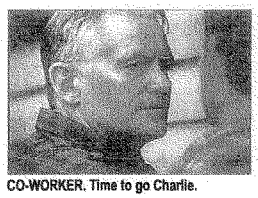
But the chemo slowed me right down.



For the first time ever, I was too tired to work.



ANNCR V.O.: If you're on chemo and feel tired, you may be anemic



CO-WORKER. Time to go Charlie.



ANNCR V.O.: Ask your doctor if PROCRIT is right for you.



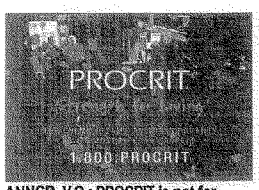
ANNCR V.O.: PROCRIT is for chemotherapy-related anemia in patients with most kinds of cancer.



PROCRIT is proven to help rebuild red blood cells, which can mean more strength.



CHARLIE OC: Okay folks, I'm back. (Auctioneering dialogue under)



ANNCR. V.O.: PROCRIT is not for patients with uncontrolled high blood pressure, and may increase the risk of blood clots.



CHARLIE O.C.:
In this business, you've got to be fast.

Anderson DDB Health & Lifestyle

PRODUCT: PROCRIT
CODE# JJNO6429
LENGTH :60
TITLE LA BODEGA - ENGLISH



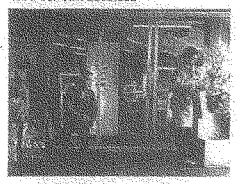
DON RAMON: We worked very hard to have our own business



So we could give our children what we didn't have ... an education.



When I got cancer, the chemotherapy made me so weak...



I couldn't believe it, my family was doing my work.



My friend told me the fatigue could be caused by anemia, and only a doctor could treat it. So, I asked my cancer specialist about PROCRIT.



VO: PROCRIT is an injection that treats chemotherapy-related anemia in patients with most types of cancer. Ask your cancer specialist if PROCRIT is right for you.
SUPER: Injectable by a cancer specialist.



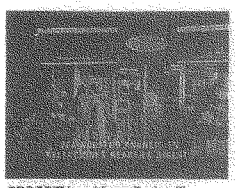
PROCRIT is proven to help rebuild red blood cells, which can mean more strength.



SUPER: More red blood cells can mean more strength.



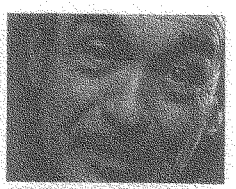
CUSTOMER: Welcome back.
SUPER: By Prescription Only.



PROCRIT is not for patients with uncontrolled high blood pressure, and may increase the risk of blood clots.
SUPER: See our ad in "Selecciones Reader's Digest".



Talk to your cancer specialist, and find out how PROCRIT can help you get back your strength for living.
SUPER: PROCRIT® Strength For living®
For chemo related anemia in patients with most kinds of cancer.



DON RAMON: Now I have the strength to keep on building their future.

Procrit– Chronology of FDA Regulation of ESA "Quality of Life" Advertising

***Note**: In the early 1980s, Amgen developed epoetin alfa, a genetically engineered copy of a human hormone, marketed under the name Epogen. But in 1985, Amgen, then a small start-up bio-tech, licensed most of its marketing rights over the drug to Johnson & Johnson. Under the licensing agreement, Amgen kept control over marketing the drug to dialysis patients with chronic renal (kidney) failure (CRF). Ortho Biotech LP (Ortho), a wholly owned subsidiary of J&J, in turn acquired the right to market and distribute the drug, under the proprietary name Procrit, for any other use in the U.S. Accordingly, Epogen and Procrit are identical drugs (epoetin alfa) but are marketed for different purposes by Amgen and Ortho (J&J) respectively.*

***Note**: Until 2003, the Advertising and Promotional Labeling Branch (APLB) in the Center for Biologics Evaluation & Research (CBER) held responsibility for oversight of DTC ads for oncology. In 2003, oversight over the advertising of Procrit moved from APLB in CBER to the Division of Drug Marketing, Advertising, and Communications (DDMAC) in the Center for Drug Evaluation and Research (CDER).*

Exh. 36 - 9/17/96 – "not approvable" letter from FDA CBER to Amgen/J&J denying application for "quality of life" indication.

- FDA stated: *"Our review has found that the clinical data collected are inadequate to draw any conclusions regarding an association of quality of life and Epoetin alfa therapy in patients receiving cancer chemotherapy ..."*

Exh. 37 - 3/02/98 – "not approvable" letter from FDA CBER to Amgen/J&J denying application for "quality of life" indication.

- FDA stated: *"In the absence of a carefully monitored, adequate and well-controlled clinical trial, conclusions about how patients would have responded in the absence of Epoetin alfa therapy cannot be drawn."*

Exh. 38 - 10/27/98 – letter from Amgen/J&J to FDA Advertising and Promotional Labeling Branch (APLB), CBER regarding proposed Procrit "quality of life" advertisement.

- company requests whether it is possible to promote "on increased energy and activity levels" based upon data collected during two trials of chemotherapy-induced anemia in cancer patients

Exh. 39- 11/6/98 – letter from FDA APLB to Amgen/J&J.

- cites Procrit ad which reads: *"Are you a chemotherapy patient? Do you feel tired all the time? Please tell your doctor. There's treatment for the tiredness.?"*

- FDA states: *"Procrit is intended, among other things, to treat anemia associated with certain chemotherapeutic regimens, not*

"tiredness" in general. This information is considered to be both false and misleading under the Act [reference section 502(a)] and the provisions described in 21 CFR 202.1(e)(6)(xviii)."

Exh. 40 - 11/20/98 – letter from Amgen/J&J to FDA APLB.

- J&J writes: *"Although we believe that the body of the advertisement implies the association of tiredness due to anemia, we will qualify in the "Head Lines" that treatment is for the tiredness associated with anemia."*

Exh. 41 - 3/30/99 – letter from FDA APLB concerning complaint about off-label promotion of Procrit at higher levels than indicated.

Exh. 42 - 5/11/99 – letter from FDA APLB concerning another complaint about off-label promotion of Procrit at higher levels than indicated.

Exh. 43- 1/24/00 – letter from Amgen/J&J to FDA CBER re renewed application for "fatigue" indication.

- company submits new data and states: *"[W]e have revised the proposed labeling text to describe these data which demonstrate increased energy, ability to conduct daily activity, and reduce fatigue. We have deleted specific reference to "Quality of Life" statements as it was felt to be broad in its connotation."*

Exh. 44 - 6/30/2000 "untitled" letter from FDA APLB to Amgen/J&J re multi-element promotional campaign for Procrit.

- FDA wrote: *"The claims made throughout the promotional materials are in violation of the Food, Drug and Cosmetic Act (Act) and implementing regulations due to expanding the use of the product as a treatment for fatigue."*

Exh. 45 - 8/9/00 letter from Amgen/J&J responding to 6/30/00 letter from FDA APLB.

- companies request presence of Seth Ray, Esq., or another attorney from the Office of the Chief Counsel in face-to-face meeting to help clarify "a consistent position for FDA."

Exh. 46 - 8/16/00 letter from Amgen/J&J referring to 7/21/00 teleconference regarding 6/30/00 letter from FDA APLB.

- Company states: *"At that time, you recommended that we discontinue all pieces that mentioned fatigue. When we questioned such a request, Mr. William Purvis stated that you did not mean all pieces, but rather, we should "look at primary vs. secondary vs. tertiary claims." Since these are not distinctions that are noted in the Act, we questioned how we would determine the category for claims in the pieces."*

Exh. 47 - 8/23/00 letter from Amgen/J&J to FDA APLB concerning FDA 6/30/00 letter.

- Company confirms postponement of meeting due to company request for presence of FDA Office of Chief Counsel representative and asks FDA to clarify a number of questions including:
  - "Please provide guidance on how a sponsor can effectively communicate to consumers about complicated disease states."
  - "Please provide definitions for primary versus secondary versus tertiary positioning of a product's indication in advertising and promotional materials."
-

Exh. 48 - 1/5/01 letter from Amgen/J&J to FDA CBER documenting FDA "willingness to change the position that was set forth in your June 30, 2000 letter..."

- J&J wrote: *"In some instances, there are market research data the support the fact that consumers understand anemia to be a laboratory value. However, they may not clearly understand the connection between the laboratory value and their general feeling of being tired. After a very useful discussion about the various ways to educate and communicate with consumers, FDA agreed that it was reasonable, in the context of consumer directed material for Procrit, to initially present information about fatigue, since this symptom is clearly recognized as being the most predominant. Thereafter, it would be acceptable to have a discussion about anemia, followed by a discussion of the specific treatment. Going forward, OBI [J&J] will carefully consider making symptom, condition and treatment claims within reasonable proximity to each other, but such must be evaluated against the appropriate communication format for the particular medium."*

Exh. 49 - 5/18/01 letter from Amgen/J&J to FDA stating intention to renew application for "quality of life" indication for cancer patients.

Note: 11/29/01 memo - from the Deputy Secretary of HHS instructing FDA that no regulatory letters could be issued until the Office of Chief Counsel (OCC) reviewed them. Before this policy change, OCC review

and approval of regulatory letters was not required. See GAO, "Prescription Drugs: Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising," November 2006 GAO-07-54 p. 3.

Note: The office of the Chief Counsel (also known as the Food and Drug Division of the Office of General Counsel, Department of Health and Human Services) is part of the Office of the General Counsel of the Department of Health and Human Services. The Chief Counsel of the Department advises the FDA Commissioner.

Exh. 50 - 12/21/01 "untitled" letter from FDA APLB to Amgen/J&J detailing numerous "false and misleading" aspects of Procrit advertising, including two DTC broadcast (TV) ads ("Anthem" and "Big Boy Bed") and requesting J&J revise advertising materials accordingly.

- FDA states: *"The tagline "Strength for Living" is misleading because it implies that Procrit improves strength and may improve survival when these outcomes have not been demonstrated by adequate and well-controlled clinical studies. ....*

- *"Claims or implications that Procrit treats weakness and fatigue, or that Procrit increases strength, are misleading. Procrit is indicated for the treatment of anemia in patients receiving chemotherapy for non-myeloid cancers. The presentations imply that Procrit would improve fatigue and weakness in any chemotherapy patient when, in fact, Procrit only has been shown to increase red blood cells in chemotherapy patients with anemia. Chemotherapy patients may have fatigue and weakness due to factors other than anemia. Thus, increasing red blood cells with Procrit would not necessarily improve a patient's condition for weakness and fatigue."*

Exh. 51 - 1/10/02 – handwritten notes of OCC meeting regarding FDA 12/21/01 "untitled letter": "DT" – Dan Troy? ; "ML" – Mike Landa?; "Seth" – Seth Ray?; "MR" – Mark Raza?

- "DT/SR – OCC looking at letter so should help"

- "DT – provide guidance to DDMAC + CBER"

- "DT – fully protected --- 1st Am Speech --- context matters – not commercial speech."

- "readjustment in thinking: presumption – may not speak presumption – you may speak"

- *"DT – as long as company stays away from saying literally S + E - OK"*

Exh. 52 - 1/25/02 letter from Amgen/J&J responding to FDA 12/21/01 letter.

- J&J writes in part: "It is *unclear how FDA reached the conclusion that the intent of the tagline "Strength for Living" was to imply that Procrit improves strength and improves survival. Clearly, there is an improvement in the symptoms associated with anemia."*

- *"Therefore, today as always, we contend that fatigue is a cardinal symptom of chemotherapy-induced anemia and the relationship between anemia and fatigue is universally accepted."*

Exh. 53 - 2/12/02 letter from Amgen/J&J responding to FDA 12/21/01 letter.

- J&J requests additional time in which to revise advertising materials and requests a meeting to discuss FDA allegations.

Exh. 54 – 4/02 Review Memorandum re Amgen/J&J response letter to CBER's 12/21/01 l letter.

- CBER objection summary: *"Claims or implications that Procrit treats weakness and fatigue, or that Procrit increases strength, are misleading. The presentations imply that Procrit would improve fatigue and weakness in any chemotherapy patient when, in fact, Procrit only has been shown to increase red blood cells in chemotherapy patients with anemia. Chemotherapy patients may have fatigue and weakness due to factors other than anemia."*
- J&J [OBP} response summary: J&J contends that *"the relationship between anemia and fatigue is universally accepted."* J&J refers to five references, which discuss quality of life and quality of life instruments that relate hemoglobin, and hematocrit levels to improved quality of life. *"Three of the five references have some association with OBP [J&J].*

Exh. 55 - 5/28/02 email within FDA from Broadnax to Byrd and Abrams regarding teleconference following day to address OCC viewpoint of Procrit advertising issues contained in FDA's 12/21/01 letter.

Exh. 56 - 5/29/02 handwritten notes entitled "TC [Teleconference] w/ DDMAC re: Procrit"

- *"Overall message fr. OCC – try to find middle ground. Fix in context rather than yanking material"*

Exh. 57 - 5/10/02 letter from Amgen/J&J stating, in part, proposed corrective actions to DTC broadcast (TV) ads;

- J&J will move tagline ["Strength for Living"] in closer proximity to approved indication.

- J&J will link symptoms to the disease and treatment.

Exh. 58 - 7/30/02 letter from FDA to Amgen/J&J finding most of J&J's proposed corrective actions acceptable.

- FDA reminds J&J; *"We again request that the tagline be repositioned to be closer to the indication as agreed during the April 11th teleconference.*

Exh. 59 – 2/27/07 email from Dan Troy (former Chief Counsel, OCC) to Jeffrey Senger (OCC) re J&J promotion of Procrit and related email chain.

- Troy wrote: *"A woman named Leah Walker from Amgen has asked for a meeting with Tom Abrams, Lesley Frank, and Mark Askine from DDMAC. They have asked for someone from OCC to be involved. It would be great if you could make sure that someone at OCC makes sure that people understand the limits of their authority."*

Note: An August 10, 2007 letter from counsel for J&J to Representatives Dingell and Stupak states in part: "Shortly before February 23, 2007, Amgen informed Ortho Biotech about a communication it had received from FDA requiring the discontinuation of all promotional activites for their ESA products. Ortho Biotech consulted with outside counsel, who later advised Jeffrey Senger, Deputy Chief Counsel, and Sheldon Bradshaw, Chief Counsel for FDA, of the agency's demand. Subsequently, Dr. Richard Pazdur of FDA's Center for Drug Evaluaion and Research clarified that the agency was requesting the Amgen and Ortho Biotech voluntarily discontinue promotional activities. For their ESA products."

Exh. 60 - June 20, 07 email from Seth Ray to Sheldon Bradshaw and Mark Raza re draft EPO Q&A for Ways and Means.

- Ray wrote: *"In the answer, I would delete clause (2) ("the fact that there was certain information concerning weakness/fatigue already in the product's labeling"). As Mark and I discovered yesterday, the quality of life (QOL) information in the Clinical Experience section of the Procrit PI only applies to the renal failure indication. [In fact, CBER turned down Amgens's supplements to add QOL claims regarding the cancer/chemotherapy indication.] In addition, a Q&A prepared by CBER makes a strong case that, because of marked differences in the nature of the renal failure and cancer/chemotherapy anemia indications, it is not reasonable to infer improved QOL from one indication to another."*

Our Reference Number: 95-1508

SEP 17 1996

N. Kirby Alton, Ph.D.
Amgen, Inc.
1840 DeHavilland Drive
Thousand Oaks, CA 91320-1789

Dear Dr. Alton:

This letter is in regard to your product license supplement for Epoetin alfa submitted under section 351 of the Public Health Service Act. Reference is also made to our information requests dated November 28, 1995, June 6, 1996, and July 22, 1996 and your responses dated January 22, 1996, March 21, 1996, June 17, 1996, July 17, 1996, July 25, 1996, and August 26, 1996.

The Center for Biologics Evaluation and Research (CBER) has completed the review of all submissions made relating to this product application. We acknowledge that this study was not designed to support a quality of life indication for Epoetin alfa in anemic patients undergoing chemotherapy of nonmyeloid malignancies. Our review has found that the clinical data collected are inadequate to draw any conclusions regarding an association of quality of life and Epoetin alfa therapy in patients receiving cancer chemotherapy and that this supplement is not approvable at this time based on the deficiencies outlined below.

1. Quality of life measurements are highly sensitive to small differences in patient care. Improved quality of life may be attributed to a recent transfusion, completion of chemotherapy, concomitant medications, the time of day the questionnaire was administered, or the fact of participating in a trial. In the absence of a carefully monitored double-blind placebo-controlled clinical trial, one cannot draw conclusions about how patients would have responded in the absence of Epoetin alfa therapy.

2. The data submitted do not constitute evidence of an association between administration of Epoetin alfa and an improvement in functional capacity parameters. The reported p-value of <0.001 gives strong evidence that the mean improvement in energy level, activity level and overall quality of life is greater than zero. This evidence does not address the question of whether Epoetin alfa can be associated with this increase, unless it is known that this population would have experienced no mean improvement in the absence of Epoetin alfa.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
DARP	Webber	9/17/96						
DTOA		9/3/96						
DAVP		9/17/96						

If you wish to pursue a Quality of Life indication for patients undergoing cancer chemotherapy, study PR 93-27-003 can not stand as a substantive part of the clinical basis for a labeling change because of the deficiencies stated above. The study might be considered minimally supportive of this indication. In that regard, we recommend you address the following:

3. Estimates of the mean improvements in energy level, activity level and overall quality of life were based upon incomplete data. Of the 261 patients who died on study, only 14 (5%) completed the questionnaires. Since the overall response rate was 75%, patients who did well were more likely to have completed the questionnaire. The estimates reported should be readjusted to correct for bias due to selective response. Please comment.

4. With reference to the manuscript by Glaspy *et al.* submitted on June 17, 1996, please address the following:

   a. Please explain the discrepancy in the number of patients who received cisplatin listed on page 8 (441) and on page 11 (492).

   b. Please submit a complete copy of the original manuscript; on the top of page 16, four sentences appear to have been deleted.

   c. Please provide ranges for the effect sizes listed on the bottom of page 16 so that their impact may be assessed.

   d. In Table 1, page 36, please include transfusion data for months 1-4.

   e. Despite differences in quality of life measurements, the patients did not demonstrate the same degree of change in either ECOG or Karnofsky Performance Scores. Please comment.

5. In item 3 of your June 25, 1996 submission, please explain the discrepancies between the table and the chart with regard to the numbers of patients treated with taxol and doxorubicin.

We reserve comment on the labeling until the application is otherwise acceptable.

You may request a meeting with CBER to discuss the above steps for approval. Please request the meeting at least 15 days prior to the proposed meeting date. Alternatively, you may choose to discuss the above steps via a telephone call. Should you wish this meeting or a telephone discussion, please call Leon Epps, in the Division of Application Review and Policy at (301) 594-5660.

Within 10 days after the date of this letter, you are requested to: (1) amend the application; (2) notify us of your intent to file an amendment; (3) withdraw the application; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, CBER may initiate action to deny the application. Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Sincerely yours,

Karen Weiss, M.D.
Director
Division of Clinical Trial Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

cc:	H. Chang, M.D.	HFM-570
	K. Weiss, M.D.	HFM-570
	J. Siegel, M.D.	HFM-500
	T. Neeman, Ph.D.	HFM-215
	P. Lachenbruch, Ph.D.	HFM-215
	S. Risso	HFM-585
	G. Jones, Ph.D.	HFM-585
	R. Wolff, Ph.D.	HFM-594
	L. Epps, Ph.D.	HFM-594
	K. Webber, Ph.D.	HFM-594

OTRR:DARP:YOFFE:8/27/96/; Epps:9/11/96(revised); Epps:9/13/96 (revised);ty:9/17/96
Webber:9/16/96(revised)
(S:\Webber\Amgen\951508.mod)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Our Reference No.: 95-1508

MAR 0 2 1998

N. Kirby Alton, Ph.D.
Amgen, Inc.
1840 DeHavilland Drive
Thousand Oaks, CA 91320-1789

Dear Dr. Alton:

This letter is in regard to your biologics license supplement for Epoetin alfa dated September 21, 1995, submitted under section 351 of the Public Health Service Act. The Center for Biologics Evaluation and Research (CBER) has completed the review of all submissions made relating to Epoetin alfa's ability to support a quality of life indication in anemic patients undergoing chemotherapy for nonmyeloid malignancies. Reference is made to our not approvable letter dated September 17, 1996 and to your response dated October 20, 1997. Our review finds that the information and data submitted are inadequate for final approval action at this time because they do not address the deficiencies outlined in questions one and two of our letter of September 17, 1996. In the absence of a carefully monitored, adequate and well-controlled clinical trial, conclusions about how patients would have responded in the absence of Epoetin alfa therapy cannot be drawn. The new and adjusted data submitted do not provide definitive evidence of an association between administration of Epoetin alfa and an improvement in functional capacity parameters.

We reserve comment on the proposed labeling until this supplement is otherwise acceptable.

You may request a meeting with CBER to discuss the above steps for approval. Please request the meeting 15 days prior to the proposed meeting date. Alternatively, you may choose to discuss the above steps via a telephone call. Should you wish this meeting or telephone discussion, please call Leon Epps, Ph.D., in the Division of Application Review and Policy at (301) 827-5103.

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the supplement; (2) notify us of your intent to file an amendment; (3) withdraw the supplement; (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of this supplement. In the absence of any of the above responses, CBER may initiate action to deny this supplement.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
DARP		2/25/98	DRP		2-26-98			
DARP		2/25/98						
DARP		12-27-98						
OLDA		2-27-98						

Page 2 - Dr. Alton

Please note our review clock has been suspended with the issuance of this letter. Note also that the any amendment should respond to all deficiencies listed and a partial reply may not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Sincerely yours,

Karen D. Weiss, M.D.
Director
Division of Clinical Trial Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

cc: H.Chang, HFM-570
T.Neeman, HFM-215
P.Lachenbruch, HFM-215
L.Epps, HFM-594
P.Keegan, HFM-573
G.Jones, HFM-585
S.Risso, HFM-500
J.Siegel, HFM-500
B.Goldman, HFM-500
M. Naecker, HFM-585
K.Weiss, HFM-570
R.Wolff, HFM-594
QAS, HFM-4

PREPARED BY:lae:2/17/98:2/20/98:sd:2/23/98:2/25/98
(*s*:\epps\95-1508.doc)

Jeffery N. Fellows
Associate Director, Regulatory Affairs

AMGEN

Amgen
1840 DeHavilland Drive
Thousand Oaks, CA 91320-1789
805.447.1000
Direct Dial
Fax

October 27, 1998

Ms.Toni Stifano
Office of Compliance and Biologics Quality/Advertising and Promotional Labeling Staff (HFM-202)
Center for Biologics Evaluation and Research
Food and Drug Administration
c/o Document Control Center (HFM-99)
Woodmont Office Center, Suite 200 North
1401 Rockville Pike
Rockville, MD 20852-1448

RECEIVED
OCT 28 1998
L98020722
CBER/DCC

RE: PROCRIT®(Epoetin alfa) Quality of Life Draft Advertisement (MIN X0186)

Dear Ms. Stifano,

This letter is in follow up to the telephone conference of Wednesday, October 14, 1998 between yourself, representatives of Amgen Inc., and The RWJ Pharmaceutical Research Institute, wherein discussions took place regarding possible agency directives on data required to support Quality of Life labeling.

During that conversation representatives of PRI inquired as to whether it would be possible to promote on increased energy and activity levels based on data collected with well-validated instruments during two large open-label trials of anemic cancer patients treated with chemotherapy.

Your advice was to provide a mock up of the a promotional piece with accurate and inclusive data, showing both positive and negative results and describing the domains measured and type of measurement instrument, patient population of study, numbers of patients evaluated, and accountability for those not evaluated.

In accordance with that advice, we are herewith providing five copies of a draft promotional piece describing increased energy and activity levels in anemic cancer patients treated with chemotherapy for review at the Quality of Life Committee meeting on October 29, 1998. Also provided are copies of the two publications from which these data are derived:

- Demetri GD, et al. Quality of life benefit in chemotherapy patients treated with Epoetin alfa is independent of a disease response or tumor type: results from a prospective community oncology study. Journal of Clinical Oncology 1998 October; 16(10):3417-3425.

- Glaspy J, et al. Impact of therapy with Epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Journal of Clinical Oncology 1997 March; 15(3):1218-1234.

Your consideration and willingness to assist us in this activity are greatly appreciated.

Should you have any questions, please contact either Heather Perritano or myself at [ ]or[ ]respectively, or by FAX at[ ]

Sincerely,

Jeffery Fellows
Associate Director, Regulatory affairs

(98_1027_hp_X0186)

NOV - 6 1998

Mr. Ralph J. Smalling
Amgen
One Amgen Drive
Thousand Oaks, CA 91320-1789

Dear Mr. Smalling:

This letter is a follow-up to a phone conversation held on November 2, 1998 between Ms. Donna Peterson and myself and will only address our concerns regarding a direct to consumer advertisement for PROCRIT® (Epoetin Alfa). The advertisement in question ran in Parade Magazine on Sunday, October 25, 1998; a copy is enclosed for your reference.

The headline for this ad reads:

"Are you a chemotherapy patient? Do you feel tired all the time? Please tell your doctor. There's treatment for the tiredness".

The header and body of this ad fails to disclose that PROCRIT is not intended for ALL patients on chemotherapy, and it is in fact limited for use by the approved labeling only for those patients with non-myeloid malignancies. In addition, PROCRIT is intended, among other things, to treat the anemia associated with certain chemotherapeutic regimens, not "tiredness" in general. This information is considered to be both false and misleading under the Act [reference section 502(a)] and the provisions described in 21 CFR 202.1(e)(6)(xviii).

Further, on a technical note, the body of the ad directs the consumer to *"see the following patient information"*, when this information is in fact a "Brief Summary". Also, the page on which the ad appears contains independent intervening material between it and the required brief summary of prescribing information which thereby results in two separate advertisements.

As discussed, I had requested that Amgen stop running this advertisement. Understanding the nature of print deadlines and lead times, we acknowledge the fact that there is a remote possibility that this ad could unavoidably appear

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
612	Rewis, W	11-6-98						

*U.S. GPO: 1988-[illegible]

in the next issue. However, we ask that you notify us in writing of the date that this ad was cancelled and note any exceptions as to its appearance.

If you have any questions or require further information or clarification, please contact me at 301-827-6096, or send any written correspondence to: Toni M. Stifano, Associate Director, Regulatory Policy, Office of Compliance and Biologic Quality, HFM-602, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852-1448.

Yours Truly,

William V. Purvis, Director
Advertising and Promotional
Labeling Staff
Center for Biologics Evaluation
and Research

Enclosure

TMS:tms:11/4/98; WVP:11/5/98
#amgendtc#3.doc

cc:
ECole HFM-600
JDonlon HFM-600
SMasiello HFM-600
FSadler HFM-48
JSiegel HFM-400
TStifano HFM-600
DCC HFM-99
Files-HFM-602
WPurvis HFM602
PKeegan HFM-573
KWeiss HFM-570
SEllenberg HFM-210

Ralph Smalling
Sr. Director, Regulatory Affairs

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789
805-447-1000
Direct Dial [redacted]
Fax [redacted]

P9030811

November 20, 1998

Toni M. Stifano
Associate Director, Regulatory Policy
Office of Compliance and Biologic Quality (HFM-602)
Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852-1448

RECEIVED
NOV 23 1998
L98022460
CBER/OCC

P980912

Ref.: PROCRIT® (Epoetin alfa) Direct to Consumer Ad (MIN X0211) and Related Ads (MIN X0192, X0195, X0210)
(P9010515, P9010518, P9010532)

Dear Ms. Stifano:

Amgen Inc. herewith confirms that pursuant to your November 6, 1998 letter, the PROCRIT® (Epoetin alfa) advertisement which ran October 25, 1998 in Parade Magazine will no longer appear in this or any other journals. Variations of the advertisement also appeared as outlined in the table below:

PROCRIT Oncology DTC Campaign Print Effort

Publication	Issue	MIN
MAMM*		
	June/July	X0192
	Aug/Sept	X0195
	Oct/Nov	X0195
Coping*		
	July/Aug	X0195
	Sept/Oct	X0210
	Nov/Dec	X0211
Time (Wrap)		
	7/13/98	X0210
	rotating	X0195
	every week**	X0192
Mature Outlook*		
	July/Aug	X0192
	Sep/Oct	X0210
Prevention		
	Jul	X0192
	Aug	X0195
Medizine		
	Fourth Quarter	X0195
Parade Full Circulation	10/25/98	X0211

* Journals issued bi-monthly
** Wrap ads rotated weekly starting 7/13/98. Ortho Biotech Inc. has ordered cessation.

Amgen wishes to comply with FDA's comments as communicated in the November 6, 1998 letter and attached advertisement, and will address these issues as appropriate in the Parade advertisement and all pieces with similar claims, as follows:

1. Reference will be included to qualify that treatment is for the anemia associated with chemotherapy for non-myeloid malignant cancers.

2. Although we believe that the body of the advertisement implies the association of tiredness due to anemia, we will qualify in the "Head Lines" that treatment is for the tiredness associated with anemia.

3. We will ensure that in the future, no copy appears between the PROCRIT® advertisement copy and the brief summary.

4. We will identify the brief summary as such and not as patient information until the time that an appropriate Patient Information Summary is available.

We appreciate CBER's constructive comments regarding this matter, and will not rerun the ads until we receive verbal or written acceptance by CBER of the above remediations. Should you have any questions or require further information, please contact either Becky Cleavenger or myself at [ ] or [ ] respectively, or by FAX at [ ]

Sincerely,

Ralph J. Smalling
Sr. Director Safety and Regulatory Affairs

(98-1120_bc_X0192 X0195, X0210, X0211)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MAR 30 1999

Ralph Smalling
Sr. Director, Regulatory Affairs
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789

Dear Mr. Smalling:

The Advertising and Promotional Labeling Staff (APLS) has received a complaint regarding a Ortho Biotech sales representative's promotion of a 40,000 unit once weekly dose of Procrit (Epoetin alfa) in anemic cancer patients on chemotherapy. A copy of all the promotional materials brought to our attention is enclosed for your reference. These materials are defined as labeling under section 201(m) of the Federal Food, Drug and Cosmetic Act (Act) and further described in 21 CFR 202.1(l)(2) of the regulations.

The following materials have purportedly been used by the sales representative to persuade hematology/oncology physicians east of the Mississippi river in changing how they prescribe Procrit for their cancer patients. A Procrit dose of 40,000 units administered once weekly is currently only indicated in surgery patients. These materials are, therefore, false, lacking in fair balance and misleading or otherwise violative of section 502(a) of the Act since they contain a representation or suggestion not approved or permitted for use in the labeling. Specifically, this promotional material directs using Procrit at a higher dose and different schedule and promotes this regimen as better, more effective and useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

Handdrawn (Homemade) Graph

This handdrawn (homemade) graph was used to illustrate how a 30,000 unit dose of Procrit administered once weekly will fall below a certain therapeutic blood level before the end of a one week interval whereas a 40,000 unit once-weekly dose will remain above this therapeutic blood level during the entire week. Both of these regimens are compared to what appears to be a "roller-coaster" blood level achieved by using 10,000 units three times weekly.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HAH-60	Broadnax	3/30/99						
GCZ	[illegible]	3/30/99						

Abstract - "Pharmacokinetics (PK) and pharmacodynamics (PD) of weekly and t.i.w. subcutaneous doses of recombinant human erythropoietin in healthy subjects."

This abstract was distributed with the above graph. It was apparently used in part to explain that clearance of recombinant human erythropoietin decreased with increasing dose. The study was done, however, only in healthy male volunteers.

Oncology Critical Pathways

This supplement to Oncology Issues was made possible by an educational grant from Ortho Biotech Inc. and was distributed by the sales representative at a luncheon held for oncology nurses and physicians. The document contains an algorithm entitled, "Clinical Pathway for Epoetin Alfa in Chemotherapy-Induced Anemia for Patients with Non-Myeloid Malignancies" in place at Georgetown University Medical Center, Lombardi Cancer Center. The algorithm uses 40,000 units of Epoetin alfa once per week as a starting dose. This document was apparently used to validate that this is a recognized method of treatment at a large cancer center and was considered significant enough to be published in this "Pathways" supplement.

Allegheny University Hospitals Memorandum with Attachments

The subject of this memorandum is weekly administration of Procrit in chemotherapy-induced anemia. Attachments to this memorandum include an algorithm for the once weekly regimen at Allegheny University Hospitals, Proposed U.P.C.I. Usage Guidelines and another algorithm in use at the University of Texas MD Anderson Cancer Center. All three algorithms use a Procrit starting dose of 40,000 units.

The use of these materials in a promotional setting raises questions as to the validity of these materials as scientific or educational in nature. Under the conditions of use described, they are regarded to be promotional labeling for Procrit and are subject to sections 502(a) and (f) and other sections of the Act.

We request that Amgen/Ortho Biotech investigate this incidence and report findings back to the APLS. We suggest that Ortho Biotech discuss this matter with their sales representatives in particular the use of handdrawn (homemade) pieces, unpublished literature and other references to promote this off-label use of Procrit.

Your prompt and direct reply is requested within ten (10) business days of your receipt of this letter. If Ortho Biotech forwards sales directives to address this incident, please enclose a copy with your response. The response should be sent to the attention of Ms. Carole Broadnax, Regulatory Review Officer, at the following address:

Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Advertising and Promotional Labeling Staff
1401 Rockville Pike, Suite 200S (HFM-602)
Rockville, MD 20852-1448

Sincerely yours,

William V. Purvis
Director, Advertising and Promotional Labeling Staff
Center for Biologics Evaluation and Research

Enclosure(s)

concurrence:
W Purvis/3-25-99/3-29-99
C Broadnax/RD 3-24-99/Edit 3-25-99/3-29-99

cc:
W Purvis (HFM - 602)
C Broadnax (HFM-602)
L Epps (HFM-594)
S Litwin (HFM-576)
P Keegan (HFM-573)
DCC
ARFS File
Address: j/apls/broadnax/procrit/QW dose complaint letter
Review No. C9021702

UNTITLED LETTER

MAY 1 1 1999

Ralph Smalling
Sr. Director, Regulatory Affairs
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789

Dear Mr. Smalling:

In follow-up to our recent correspondence dated March 30, 1999, and April 26, 1999, regarding an Ortho Biotech Inc. (OBI) sales representative's off-label promotion of Procrit (Epoetin alfa) 40,000 units once weekly dosing in anemic cancer patients on chemotherapy, another complaint about this same issue has been brought to the attention of the Advertising and Promotional Labeling Staff (APLS). A copy of the promotional material is enclosed for your reference. These materials are defined as labeling under section 201(m) of the Federal Food, Drug and Cosmetic Act (Act) and further described in 21 CFR 202.1(l)(2) of the regulations.

Information provided to the APLS indicates that the promotional material, an algorithm for the weekly administration of Procrit 40,000 units in cancer patients, was used by the sales representative to discuss this off-label use with an oncology physician west of the Mississippi river. The sales representative visited the physicians office around the second or third full week of April 1999, which is the same timeframe that two directives dated April 9, 1999, and April 16, 1999, were issued by OBI to its sales representatives.

As you previously stated in your April 20, 1999, letter, we reemphasize that OBI continue to reinforce their policy and FDA requirements as outlined in that letter during future training sessions for the sales representatives. Please provide us with the dates for training sessions where this issue will be discussed.

rILE
COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFD-[illegible]	Bradner	5/4/99						
602	Purvis, W	5/11/99						

Your prompt and direct reply regarding OBI's promotion is requested within ten (10) business days of your receipt of this letter. The response should be sent to the attention of Carole Broadnax, R.Ph., Regulatory Review Officer, at the following address:

Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Advertising and Promotional Labeling Staff
1401 Rockville Pike, Suite 200S (HFM-602)
Rockville, MD 20852-1448

Sincerely yours,

William V. Purvis
Director, Advertising and Promotional Labeling Staff
Center for Biologics Evaluation and Research

Enclosure

concurrence:
W Purvis/5-11-99
C Broadnax/RD 5-6-99/Edit 5-11-99

cc:
Original - DCC (HFM-99)
FOI (HFM-48)
APLS Reading File (HFM-602)
APLS Letter File (HFM-602)
L Epps (HFM-594)
S Litwin (HFM-576
P Keegan (HFM-573)

Address: j/apls/broadnax/procrit/kral qw dose complaint
Review No. C9050306

Senior Director, Regulatory Affairs
Karen's Copy

January 24, 2000

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789
805.447.1000
Direct Dial [ ]
Fax [ ]

Glen Jones, Ph.D.
Division of Application Review and Policy HFM-585
Food and Drug Administration
Center for Biologics Evaluation and Research
c/o Document Control Center, Suite 200N
1401 Rockville Pike
Rockville, MD 20853-1448

Meeting Request
Type B (Pre-BLA)

000396320



Epoetin alfa Product License
Reference No. 95-1508, Quality of Life in Cancer Patients

Dear Dr. Jones:

Reference is made to the 23 September 1998 meeting between Amgen Inc., Ortho Biotech Inc. and the Agency to discuss Epoetin alfa in regard to the "Quality-of-Life" data for anemic patients undergoing chemotherapy for non-myeloid malignancies. Reference is also made to the Agency's 02 March 1998 letter regarding this supplement. The date of the original submission was 21 September 1995 (Ref. No: 95-1508).

At this time we are providing the Meeting Minutes/Memorandum of Understanding from the 23 September 1998 meeting (overheads used during this presentation available upon request).

Data are now available from a Multinational, Multicenter, Phase III, Placebo Controlled Study in Cancer Patients (INT-10) which we would like to discuss with the Agency. Information on this study will be included as part of the Background Document. This double-blind, placebo-controlled study assessed the effect of early intervention and/or treatment with Epoetin alfa on anemia in cancer patients receiving non-platinum containing chemotherapy. [redacted] The changes in these particular domains are consistent with the Phase IV, Open Label, Multicenter Trials that we have previously presented.

A statistical reanalysis of the Phase IV data provided by Dr. Stan Finkelstein (MIT-Sloan School of Management) will be included in the Background Package as well as an analysis from Dr. Janet Wittes (Statistical Collaborative, Inc.) on the relationship between hemoglobin and quality of life in the Phase IV studies.

JAN 28 2000
L10466

In addition and as discussed during our 23 September 1998 meeting, we will be providing reanalyzed quality-of-life data from the original, Phase III, Placebo Controlled Studies in Cancer Patients. These data, which included quality-of-life parameters, were initially submitted on 29 July 1991 and were reanalyzed based on questions received from the Agency regarding source of the bulk material. Data derived only from Amgen-sourced bulk material were re-submitted on 31 July 1992 and these data subsequently provided the support for the approval of the cancer indication. Because clinical experience has demonstrated clinical equivalence between Epoetin alfa, regardless of source, we are summarizing the original study results collected for Quality of Life for patients who received chemotherapy as supportive data. Also, brief synopses of four additional supportive studies will also be included.

Finally, we have requested Dr. Donald Patrick from the University of Washington, Seattle, Washington, to evaluate the Quality of Life data from our Phase III (Int-10) and Phase IV data, and summarize its merits in the form of an Expert Report. Dr. Patrick's evaluation will be included in the Background Document for your review.

As suggested by Dr. Jay Siegel and the Agency at the 23 September 1998 meeting, we have revised the proposed labeling text to describe these data which demonstrate increased energy, ability to conduct daily activity, and reduce fatigue. We have deleted specific reference to "Quality of Life" statements as it was felt to be broad in its connotation. This draft text is included for your review and comment.

If there are any questions, please call me at [redacted] or Donna Peterson at (805) 447-4966. Amgen considers the contents of this submission confidential and exempt from disclosure under 21 CFR 20.61.

Sincerely,

For Ralph Smalling
Sr. Director
Regulatory and Medical Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

JUN 30 2000

Mr. Ralph Smalling
Sr. Director, Regulatory Affairs
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789

Dear Mr. Smalling:

The Advertising and Promotional Labeling Branch (APLB) in the Office of Compliance and Biologics Quality has reviewed a multi-element promotional campaign by Ortho Biotech Inc. (OBI) for the product Procrit (Epoetin alfa). Amgen, Inc. is the license holder for Procrit and is responsible for the distribution of all advertising and promotional material for the product.

The claims made throughout the promotional materials are in violation of the Food, Drug and Cosmetic Act (Act) and implementing regulations due to expanding the use of the product as a treatment for fatigue. These claims also appeared on the www.Procrit.com website as recently as April, 19 and 20, 2000. In addition, there are some questions regarding Amgen's and or OBI's relationship with the National Minority Aids Council (NMAC) and The Balm in Gilead regarding the promotion of Epoetin alfa for the treatment of HIV anemia and tiredness. We also have concerns over the proper submission of advertising and promotional labeling material to APLB as required by the regulations. Copies of the promotional labeling material, website and NMAC/Gilead materials are enclosed for your reference.

I) Examples of the false and/or misleading claims and the lack of fair balance include:

Finding Strength: A Program for Managing Cancer-Related Fatigue and Anemia for Patients and Their Families – Patient Education Video - Manufacturer's ID No. X0417

"Fatigue is one of the common side effects of chemotherapy".
"There may always be some fatigue with cancer and cancer therapy but it can be helped."

These claims suggest that Procrit is to be used for the treatment of fatigue. The information provided under "What is Procrit?" fails to balance the theme that Procrit treats fatigue.

Oncology TIME Wrap – Manufacturer's ID No. X0401

"If you're a chemotherapy patient...feel tired...a way for you to overcome your fatigue".

This claim suggests that Procrit can be used for the treatment of fatigue. The subsequent information fails to balance this open-ended and unqualified statement. In addition, the wrap states the limitation of use for Procrit but lacks adequate fair balance. The full indication should be stated. Also, the wrap asks the reader to, "Please see the following Prescribing Information." The information in fact is a Brief Summary of Prescribing Information and not the required full prescribing information. This was previously brought to Amgen's attention in a letter dated November 6, 1998.

Ralph Smalling - Page 2

Immunology Interactive Banner – Manufacturer ID No. X0398

"A low red blood cell count can make you tired and weak"
"…HIV and HIV meds can deplete your body's red blood cells and cause anemia. And anemia can make you feel tired and weak."

The first statement makes an inappropriate analogy between low red blood cell counts and tiredness and weakness that suggests that Procrit can be used to treat tiredness and weakness. The second statement inappropriately refers to HIV medications in general. Procrit is specifically indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients and not related to general therapy with HIV medications.

Supplement to Readers' Digest – Manufacturer ID No. X0395

Page 2 – "… treating chemotherapy-related fatigue, a major problem for many patients."
Page 2 – "Q: Can anemia cause symptoms that could affect my quality of life?"
"A: … fatigue, caused largely by chemotherapy-induced anemia is a top concern for patients."
The statement and the question and answer are potentially misleading in that they suggest an association between Procrit and fatigue and that Procrit is indicated for improvement of quality of life.

Page 3 – "Q: How can I help my fatigue?"
The logo/graphic above this question suggests that Procrit is the answer.

Page 3 – "In fact, I begin treatment with PROCRIT when a patient's hemoglobin is just below normal so the person never suffers truly debilitating fatigue and responds to the drug more quickly."
This statement suggests the treatment of fatigue and not the treatment of anemia.

Page 4 – "Fighting Fatigue at the Source"
This statement suggests that Procrit will help alleviate fatigue. In addition, the narrative falsely states that "Without good oxygen flow, you can't maintain your energy levels and you become anemic…." This statement is incorrect, loss of red blood cells causes anemia.

Page 5 – "Fatigue is a Fact"
While the text below this subheader discusses the anemia experienced by chemotherapy patients, this subheader focuses on fatigue.

Fatigue Slim Jim – Fatigue Survey: Anemia and Fatigue in Patients with Cancer – Manufacturer ID No. X0357

This title suggests a discussion of anemia and it's association with cancer patients. However, the narrative discusses fatigue as a major side effect of cancer. This piece does not adequately describe the link between chemotherapy, anemia and fatigue. In addition, this slim jim uses two peer-reviewed journals as support, but the majority of the claims are referenced to "Data on File" at OBI. Ortho Biotech Oncology endorsement may suggest Procrit treats fatigue.

Tabletop display panels: "Committed to Enhancing..." – Manufacturer ID No. X0349

"Committed to Enhancing Quality of Life Through Research"
"Treat All Tumor Types With the Same Confidence"
"Fatigue: A Widespread, Debilitating Condition," and underlying referenced text.
These claims fail to adequately state that Procrit is indicated for the treatment of anemia. They also suggest that Procrit is used for the treatment of tumors, fatigue and for the improvement of quality of life. Only on top of the fourth panel in small print is the indication for Procrit provided, "For Anemic Patients with Nonmyeloid Malignancies".

Nephrology Patient Education take-one brochure – Manufacturer. ID No. X0332

"Talk to your doctor about fatigue. ... Your doctor can determine which treatment is best...."
These statements imply that Procrit is approved to treat fatigue.

Website – April 19 and 20, 2000

The overall theme of this site promotes a broader use for Procrit than for which it is indicated. It should clearly state that Procrit is indicated for the treatment of anemia in certain patient populations and not for the general treatment of tiredness or fatigue. Examples of claims that suggest Procrit treats fatigue include:

Procrit Homepage:
"Welcome – If you're looking for the latest news on fatigue and anemia, you've just found it.
HIV/AIDS subheading - "Learn how tiredness associated with HIV-related anemia can be treated."
Cancer subheading – "Anemia-related fatigue, a common chemotherapy side effect, can be treated."
" For chemotherapy patients, with anemia and fatigue."
Directly under each subheading, "HIV/AIDS, Cancer, Surgery and Early Kidney Disease," the full indication statement should be clearly stated.

HIV/AIDS Homepage:
This page begins with a discussion about people with HIV and AIDS being tired and fatigued before discussing one of the most common causes of fatigue, anemia. At the end of the page, the focus is again on fatigue with the statement, "...fatigue is becoming a key quality of life issue." The last paragraph also suggests that Procrit treats fatigue by claiming, "Procrit increases the production of red blood cells, improving anemia, and helping ease the symptoms of fatigue, and raising energy levels."

Cancer Homepage:
This page also begins with a discussion focusing on fatigue before stating that "feeling unusually tired may be due to anemia, a common side effect of many chemotherapy regimens." The page continues with, "If you are concerned about weakness and fatigue following chemotherapy, learn more by visiting other areas of this site...and ... about how PROCRIT (Epoetin alfa) works."

The claims above are similar to a previous objectionable advertising theme that was outlined in the Advertising and Promotional Labeling Staff's (APLS) November 6, 1998, letter to Amgen regarding a direct to consumer advertisement in Parade Magazine. This current campaign fails to properly emphasize that Procrit is for the treatment of anemia. Furthermore, based on this campaign, we do not regard your attempt to qualify that treatment with Procrit is for the tiredness associated with anemia as being effective in properly conveying the product's approved indications.

II) National Minority Aids Council (NMAC) and The Balm in Gilead

A NMAC brochure entitled, "You Don't Have to Feel So Tired – Treating HIV-Related Anemia" was obtained from a Washington, D.C. area AIDS clinic on or around May 16, 2000. This brochure mentions Epoetin alfa on page 2 under the "How is Anemia Treated?" subheading. In addition, a poster sponsored by NMAC and The Balm in Gilead showing Dr. Joycelyn Elders, Former U.S. Surgeon General standing with two men who are living with HIV was obtained from the AIDS clinic at the same time. The three are holding a placard that states, "FORMER SURGEON GENERAL'S ADVICE: Treat HIV-Related Anemia and Re-Energize Your Life! See Your Doctor or Call 1-888-321-AIDS Today." The bottom of the poster quotes Dr. Elders as saying "For too long, people with HIV-related anemia have been feeling especially tired ... Get the proper treatment and you can get your energy back." After calling the 1-888 number, option number 3 mentions Epoetin alfa as a treatment option.

In light of OBI's multi-element promotional campaign, there is some question as to Amgen's and or OBI's involvement with NMAC and The Balm in Gilead in the creation of the brochure and the poster. It is FDA's position that where there is a direct link to a manufacturer's product and the NMAC or The Balm in Gilead is being paid by the manufacturer to produce these materials, then NMAC and The Balm in Gilead are acting as agents for the manufacturer. The manufacturer is then responsible for the entire content of the material. Please provide information regarding Amgen's and/or OBI's relationship with the NMAC and The Balm in Gilead and Amgen's and/or OBI's control or influence over the content of the brochure and poster.

III) Appropriate Submission of Advertising and Promotional Labeling Material

The regulations require the submission of copies of advertisements and promotional labeling at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement. Some of the materials mentioned above were submitted as much as nine months after initial dissemination or publication. For example, the Immunology Interactive Banner (MIN X0398) was distributed July 1999, but was submitted March 31, 2000. For some of the submissions an actual day of distribution is provided but for others only the month and year are provided. With only the month and year, it is difficult to determine when the piece was distributed. Both Form FDA 2567 and 2253 request the date the labeling was initially distributed or the date of first use. This date has been commonly interpreted to mean the month, day and year. The tardy submission of materials is not acceptable and should be immediately corrected.

The concerns outlined in this letter may not reflect all of the claims that were found to be objectionable. It is Amgen, Inc and OBI's responsibility to assure that all advertising and promotional labeling is in compliance with the Act and the associated regulations.

We request that OBI immediately stop distribution of any and all materials with these or similar objectionable claims. Please account for any remaining materials in distribution channels for which OBI has control. These materials should be returned to OBI and not used. APLB requests that you immediately reassess the direction of any replacement campaign to more accurately bring in Procrit's approved use rather than an open-ended general discussion on the symptoms of fatigue and tiredness which may misleadingly suggest an unsubstantiated use for the product. In addition, the replacement campaign should address the other violations described in this letter.

Your prompt and direct reply regarding OBI's promotion of these materials is requested within fifteen (15) business days of your receipt of this letter. The response should be sent to the attention of Mr. William V. Purvis, Chief, Advertising and Promotional Labeling Branch, at the following address:

Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
Advertising and Promotional Labeling Branch, HFM-602
1401 Rockville Pike
Rockville, MD 20852-1448
(301) 827-3028

Sincerely yours,

Mary A. Malarkey
Acting Director
Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosure(s)
cc: Ortho Biotech Inc.

concurrence:
W Purvis/4-27-00/5-5-00/5-12-00/5-17-00/6-13-00/6-22-00/6-23-00/6-26-00/6-28-00
C Broadnax/RD 4-26-00/Edit 4-28-00/5-8-00/5-16-00/5-19-00/5-2500/6-12-00/6-13-00/6-21-00/6-23-00/6-28-00/6-29-00
R Steffen/5-22-00
R Rieves/5-23-00
S Litwin/5-23-00
M Malarkey/6-20-00/6-29-00

cc:
DCC (HFM-99)
FOI (HFM-48)
M Malarkey (HFM-610)
Clip Board (HFM-610)
B Browne (HFM-610)
W Purvis (HFM - 602)
C Broadnax (HFM-602)
W Schwieterman (HFM-582)
R Rieves (HFM-576)
M Walton (HFM-576)
P Keegen (HFM-573)
R Steffen (HFM-573)
S Litwin (HFM-573)
K Weiss (HFM-570)
L Epps (HFM-594)
G Jones (HFM-585)
R Klein (HF-12)

Address: j/old oeips/apls/broadnax/procrit/fatigue complaint letter – final.doc
Review No. C0022403

Vice President
Regulatory/Medical Affairs

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.1000
Direct Dial [redacted]
Fax [redacted]

August 9, 2000

Ms. Carole Broadnax
US Food and Drug Administration
Center for Biologics Evaluation and Research
Division of Case Management
Advertising and Promotional Labeling Branch, HFM-602
1401 Rockville Pike
Rockville, Maryland 20852

Dear Ms. Broadnax:

Reference is made to your letter dated August 2, 2000, in response to our letter dated July 25, 2000, requesting a formal meeting with the Food and Drug Administration (FDA). Further reference is made to a separate correspondence also dated July 25, 2000, and our teleconference that preceded the July 25, 2000 letters. Our objective throughout this process has been to understand FDA's application of the advertising provisions of the Federal Food, Drug, and Cosmetic Act and the implementing regulations, to the pieces cited in your June 30, 2000 letter.

To this end, we very much appreciate your willingness to meet and are hopeful that the meeting will serve as a forum for clarifying many of the legal, regulatory, and policy issues that were raised in your letter. Since it is important that all issues are considered at the meeting, we are requesting that Seth Ray, Esq., or, if he is unavailable, another attorney from the Office of the Chief Counsel is present. We believe that an agency attorney with broad advertising experience across Centers will be helpful in clarifying a consistent position for FDA on many of the issues raised in your letter.

We appreciate your willingness to consider this addition to your list of attendees.

Should you have any questions or require further information, please contact either Becky Cleavenger or myself at [redacted] or [redacted] respectively, or by FAX at [redacted].

Sincerely,

for/ Ralph Smalling
Vice President, Regulatory and Medical Affairs

AUG 11 2000
27491

2000-0809_BC_GC_ OBI-CBERMtg

Enclosures
Copy/ Enclosures to: Margaret Porter, Esq.
Chief Counsel, FDA

000362064

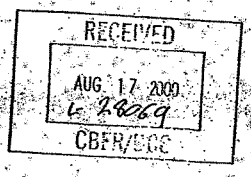
Vice President
Regulatory/Medical Affairs

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805-447-1000
Direct Dial
Fax

August 16, 2000

Ms. Carole Broadnax
US Food and Drug Administration
Center for Biologics Evaluation and Research
Division of Case Management
Advertising and Promotional Labeling Branch, HFM-602
1401 Rockville Pike
Rockville, Maryland 20852



Ref: Procrit® (Epoetin alfa) promotional materials

Dear Ms. Broadnax:

I am writing to you regarding the August 24, 2000 meeting requested by Amgen Inc. to discuss the untitled letter and subsequently returned FDA Form 2567s from FDA's Office of Compliance and Biologics Quality to Amgen regarding a multi-element promotional campaign by Ortho Biotech Inc. As you know, Ortho markets Procrit® (Epoetin alfa) through a product license agreement with Amgen. Ortho has recently asked Amgen to transmit the following comments for your consideration prior to next week's meeting:

Ortho Biotech Inc. is in receipt of your August 8, 2000 correspondence, including 16 Form FDA 2567s, which referenced promotional material for Procrit® (Epoetin alfa). We appreciate your thorough review of the promotional pieces and the comments that you provided on pieces that, in some instances, were initially used in early to mid-1999.

201.12(f)(4) & 314.81(b)(3) In attempting to address the statements made in the "Comments" section of the referenced forms, we are having difficulty reconciling your comments with the Federal Food, Drug, and Cosmetic Act (Act) and the implementing regulations. For example, the comment, "Discontinue distribution of this material until all issues with the Advertising and Promotional Labeling Branch's letter dated June 30, 2000, are resolved. Even though no product name is mentioned it is hard to separate this piece from the rest of the campaign." Since you have acknowledged that the piece is unbranded, the basis for FDA's objection is unclear.

As you will recall, concerns regarding issues raised in your June 30, 2000 letter were discussed during a teleconference on July 21, 2000. At that time, you recommended that we discontinue all pieces that mentioned fatigue. When we questioned such a request, Mr. William Purvis stated that you did not mean all pieces, but rather, we should "look at primary vs. secondary vs. tertiary claims." Since these are not distinctions that are noted in the Act, we questioned how we would determine the category for claims in the pieces. After some discussion, it was our understanding that we would clarify these and other points at a meeting and, until such time, a determination regarding the appropriate action for specific pieces would be



postponed. If these conclusions are incorrect, we would appreciate a clarification regarding your recollection of the outcome of the teleconference.

It is important to reiterate that we want to cooperate with FDA in resolving these issues. We are grateful for the opportunity to meet with representatives from the Center for Biologics Evaluation and Research. During the meeting, we would welcome the opportunity to review the agency's qualitative and quantitative consumer-related data.

If you wish to discuss these issues with Ortho and Amgen before our scheduled August 24, 2000 meeting, please contact either Becky Cleavenger or myself at [redacted] or [redacted] respectively, or by FAX at [redacted]

Sincerely,

for Ralph Smalling
Vice President, Regulatory and Medical Affairs

2000-0816_BC_GC_OBI2567Response

Enclosures
Copy/ Enclosures to: Margaret Porter, Esq.
Chief Counsel, FDA

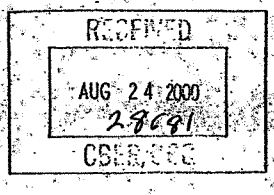
...ph Smalling
...e President
Regulatory/Medical Affairs

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.1000
Direct Dial
Fax

August 23, 2000

Ms. Carole Broadnax
US Food and Drug Administration
Center for Biologics Evaluation and Research
Division of Case Management
Advertising and Promotional Labeling Branch, HFM-602
1401 Rockville Pike
Rockville, Maryland 20852



Ref: Procrit® (Epoetin alfa) promotional materials

Dear Ms. Broadnax:

I am writing to you regarding the meeting requested by Amgen Inc. to discuss the untitled letter and subsequently returned FDA Form 2567s from FDA's Office of Compliance and Biologics Quality to Amgen regarding a multi-element promotional campaign by Ortho Biotech Inc. As you know, Ortho markets Procrit® (Epoetin alfa) through a product license agreement with Amgen. Ortho has recently asked Amgen to transmit the following comments for your consideration prior to the meeting:

Reference is made to a telephone conversation on August 17, 2000, between Mr. William Purvis and you, representing the Food and Drug Administration (FDA), and Becky Cleavenger, representing Amgen. The intent of the phone call was to convey to Amgen that the proposed meeting date of August 24, 2000, would be changed, in light of our request for representation from FDA's Office of the Chief Counsel. There were several other issues discussed during the conversation, including FDA's request for a meeting package that would include copies of all overheads and supporting data that we plan to present at the meeting. In addition, you acknowledged that FDA's allegation in the June 30, 2000 letter that our Oncology Time Wrap advertisement violated the law was incorrect. Both of these issues will be addressed below.

Regarding the meeting package, please be advised that we do not intend to present any overheads during the meeting. Our objective is to participate in a dialogue around the legal and regulatory issues cited in your letter. In keeping with this focus, we will have no clinical representation at the meeting (See Attachment 1: Revised List of OBI/Amgen Attendees). By the end of the meeting, we hope to have a better understanding of FDA's interpretation of the Federal Food, Drug, and Cosmetic Act and the implementing regulations, as it applies specifically to the cited Procrit® promotional pieces, and, generally, to other advertising and promotional labeling pieces across Centers. As a starting point for our discussion, we have enclosed a list of general, as well as specific issues/questions that we wish to discuss (See Attachment 2). As we exchange viewpoints on these importar we anticipate that additional questions will be raised.



Regarding your comments on our Oncology Time Wrap, we are very appreciative of your willingness to reconsider your original position on this piece. While we recognize that the referenced piece may no longer be an issue, it is important to correct for the record, your statements regarding our claim; "Please see the following Prescribing Information." We believe this statement is not only accurate, but also consistent with the law. It clearly does not direct the reader to the **full prescribing information.** Since the law does not mandate the precise language that can be used when directing a reader to a brief summary of prescribing information, we question why FDA is being prescriptive as it relates to this statement. Pharmaceutical companies have employed many different means for conveying such information. (See, e.g., *Reader's Digest*, August 2000).

We want to reiterate that we wish to work cooperatively with FDA to address the allegations made in your June 30, 2000 letter. We are certain that engaging in a meaningful dialogue regarding the agency's interpretation of the advertising provisions will help to clarify many of our legal, regulatory, and policy concerns.

Should you have any questions or concerns, please contact either Becky Cleavenger or myself at [ ] or [ ] respectively, or by FAX at [ ].

Sincerely,

for Ralph Smalling
Vice President, Regulatory and Medical Affairs

2000-0823_BC_GC_ OBIMtgPkg

Enclosures
Copy/ Enclosures to: Seth Ray, Esq.
Office of the Chief Counsel

Attachment 1

Revised List of Amgen and OBI Attendees

Tracy L. Acker, PharmD.	Director, Regulatory Affairs, FDA Liason, RWJPRI
Robert Church, J.D.	Corporate Counsel, Amgen Inc.
Becky Cleavenger	Manager, Regulatory Affairs, Amgen Inc.
Minnie Baylor-Henry, RPh., J.D.	Sr. Director, Regulatory Affairs, Advertising and Promotion Review, RWJPRI
Freddy Jimenez, Esq.	General Attorney, J&J Law Dept., J&J
Jean O'Connor, MS.	Sr. Director, Regulatory Affairs, RWJPRI
Shelley Reagan	Asst. Director, Regulatory Affairs, Advertising and Promotion Review, RWJPRI
Liz Scull	Director, Marketing Integration/Strategy, OBI

Attachment 2

General Questions

1. Please provide guidance on how a sponsor can effectively communicate to consumers about complicated disease states.

2. Guidance is needed regarding the FDA methodology employed and the results obtained from FDA consumer-directed research.

3. Please distinguish the circumstances that would trigger a comment on a FDA 2567 versus a letter or telephone call. What is the sponsor's obligation under each circumstance?

4. Please explain the CBER adherence to the "linkages" policy, which was abandoned by CDER approximately three years ago. In addition, please identify any other policies in which CDER and CBER differ.

Specific Questions

1. Are there circumstances in which CDER and CBER classify advertising and promotion differently?

2. Is promotion via a Kiosk advertising or labeling?

3. Is it FDA's position that in all circumstances the full indication must appear on the web-site home page?

4. Is it FDA's position that language in a company web-site is to be written in language understandable to the consumer?

5. Please provide definitions for primary versus secondary versus tertiary positioning of a product's indication in advertising and promotional materials.

6. Under what circumstances would the reference to "Data on File" or, use of the company logo brand an unbranded educational piece?

Attachment 3

Examples of Different Ways of Stating Trigger to Brief Summary

Source: Reader's Digest, August 2000

Please see next page for patient prescribing information	Meridia
Please see adjoining patient information	Visudyne
Please see important information on following pages	Flonase
Please see important information on next page	Sonata
Please read important product information on the following page and discuss it with your doctor	Prilosec
Please see important additional information on adjacent page	Lipitor
Please see next page for additional important information	Prevacid
Please see important information about Zyrtec 5-mg and 10-mg tablets and 1-mg/mL syrup on the adjacent page	Zyrtec
Please see additional important information on next page	Allegra

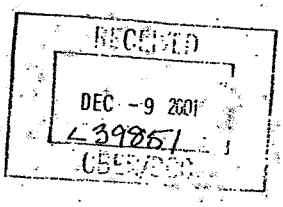
Vice President
Regulatory/Medical Affairs

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.1000
Direct Dial [redacted]
Fax [redacted]

January 5, 2001

Toni M. Stifano
Associate Director for Regulatory Policy
US Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Suite 200
Rockville, Maryland 20852-1448

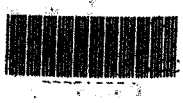


RE: PROCRIT®(Epoetin alfa) Promotional Materials

Dear Ms. Stifano:

I am writing to you regarding the October 19, 2000 conference call between CBER representatives and employees of Amgen Inc. and Ortho Biotech Inc. As you know, Ortho markets Procrit® (Epoetin alfa) through a product license agreement with Amgen. Ortho has drafted the following summary of the meeting and has asked Amgen to transmit it to you for your consideration:

> Reference is made to a telephone conference call on October 19, 2000, between William Purvis, Carole Broadnax, Mary Malarkey, and you, representing the Food and Drug Administration (FDA); Becky Cleavenger and Robert Church, representing Amgen; and Liz Scull, Shelley Reagan, Freddy Jimenez, and Minnie Baylor-Henry, representing Ortho Biotech (OBI). The primary purpose for the call was to obtain a better understanding of the Center for Biologics Evaluation and Research's (CBER) interpretation of the advertising and labeling provisions in the Federal Food, Drug, and Cosmetic Act and applicable regulations (Act). After gaining a better understanding of the general legal and regulatory framework for CBER's decisions, it was important to discuss FDA's consistent application of the law to the specific promotional pieces that were cited in a June 30, 2000 untitled letter. While there have been numerous correspondences between FDA and Amgen since the June 30, 2000 letter, FDA's scheduling difficulties prevented us from having a discussion with all of the necessary parties at an earlier time. In spite of the delay, OBI believes that the call was very productive and appreciate your willingness to provide OBI with the opportunity to participate in an important dialogue session.
>
> The following represents OBI's summary of the important issues discussed during our October 19, 2000 teleconference:
>
> FDA provided feedback on general, as well as specific, promotional issues that have a direct impact on the promotional pieces cited in the June 30, 2000 letter.



This discussion included, but was not limited to, CBER's acknowledgement that consistent with the Center for Drug Evaluation and Research's position, CBER would no longer adhere to a broad sweeping "linkages" position, when evaluating individual promotional pieces. This discussion, along with other discussions about the value of market research, helped to shape the framework for a more directed discussion about the specific pieces that FDA had previously questioned.

OBI believes that it is highly important to communicate with consumers in language that is easily understood by the intended audience. (See, An Overview of DTC Advertising and Consumer Education Articles) In looking specifically at Procrit®, there are some additional challenges that OBI encounters, when it considers how to shape an educational effort for consumers. (See, Examples of Market Research Findings) In some instances, there are market research data that support the fact that consumers understand anemia to be a laboratory value. However, they may not clearly understand the connection between the laboratory value and their general feeling of being tired. After a very useful discussion about the various ways to educate and communicate with consumers, FDA agreed that it was reasonable, in the context of consumer directed material for Procrit®, to initially present information about fatigue, since this symptom is clearly recognized as being the most predominant. Thereafter, it would be acceptable to have a discussion about anemia, followed by a discussion of the specific treatment. Going forward, OBI will carefully consider making symptom, condition and treatment claims within reasonable proximity to each other, but such must be evaluated against the appropriate communication format for the particular medium. Further, the placement of the claim must be decided on a case-by-case basis, in light of the unique characteristics of the individual piece.

FDA also requested that OBI provide information about its relationship with the National Minority AIDS Council and The Balm in Gilead. Please be advised that OBI has provided these organizations with educational grants.

The last discussion item was the issue of post-marketing reporting. Like FDA, OBI recognizes the importance of complying with 21 CFR 314.81. It is because of this commitment that OBI initiated an internal quality assurance program many months before the referenced June 30, 2000 letter. It was the outcome of this process that triggered the untimely submissions to FDA. OBI has concluded this phase of its quality program and, as discussed during our teleconference, the remaining untimely pieces will be submitted shortly under separate cover. While there has always been a procedure in place to determine compliance in the area of post-marketing reporting, OBI has instituted additional safeguards to monitor the process more closely.

In closing, OBI wants to thank you, as well as Ms. Malarkey, Mr. Purvis, and Ms. Broadnax for your consideration of OBI's position regarding the cited promotional pieces. Your willingness to change the position that was set forth in your June 30, 2000 letter goes a long way towards supporting your statements about CBER's commitment to working with the pharmaceutical and biotechnology industry to resolve differences of opinion. You also are to be commended for your public comments during the October 2000 Drug Information Association

meeting, where you stated that CBER had learned some important lessons from the Procrit® promotional discussion.

If you have any questions about the preceding summary or require further information, please contact either Becky Cleavenger or myself at [ ] or [ ] respectively, or by FAX at [ ]

Sincerely,

/s/ Ralph Smalling
Vice President, Regulatory and Medical Affairs

2001-0105_BC_GC_ConfCallMins

Enclosures

DUPLICATE

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.1000
Direct Dial [redacted]
Fax [redacted]

18 May 2001

Glen Jones, Ph.D.
Division of Application Review and Policy HFM-585
Food and Drug Administration
Center for Biologics Evaluation and Research
c/o Document Control Center, Suite 200N
1401 Rockville Pike
Rockville, MD 20853-1448

CD-ROM Demos
Quality of Life
Meeting Minutes

Attn: Mr. Charles McKeever

Epoetin alfa Product License
Reference No. 95-1508, Quality of Life in Cancer Patients

Dear Dr. Jones:

Reference is made to a CD-ROM demo submitted 17 January 2001 and to the 28 March 2001 teleconference, requested by the Agency to discuss the revised CD-ROM demo for the Quality of life submission.

As per Mr. McKeever's request during the teleconference, we submit herein, minutes to the 28 March 2001 meeting, which include the list of attendees (Attachment 1).

As agreed upon, it is our intention to revise and re-submit the Quality of life demo based on the comments raised during our teleconference. We will notify Mr. McKeever directly by e-mail, mckeeverc@fda.gov, phone number is 301-827-5101, upon its completion and re-submission.

Your review and comment of the CD-ROM demo is greatly appreciated. If you need further information, please contact Mary Boulware, at [redacted]

Sincerely,

Mary Boulware

Mary Boulware
Associate Manager
Regulatory Affairs

000773940

MAY 2 [illegible]
52606

Desk copy: Mr. Charles McKeever

Confidential Ortho Information
This information is confidential and disclosed subject to the limitations of use contained in paragraph 6.01 of the September 30, 1985 Product License Agreements between Ortho and Amgen and between Ortho and Kirin-Amgen and cannot be used for any purpose outside those agreements.

①

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

December 21, 2001

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

Mr. Ralph Smalling
Vice President, Regulatory and Medical Affairs
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Smalling:

This letter concerns Ortho Biotech Inc.'s (OBI) promotional materials for Procrit (epoetin alfa) for injection. The Advertising and Promotional Labeling Branch (APLB) in the Office of Compliance and Biologics Quality has reviewed two direct-to-consumer (DTC) broadcast advertisements ("Anthem" and "Big Boy Bed"), three DTC print advertisements (MIN X0590 and MIN X0723 – two advertisements), a professional print advertisement (MIN X0584), and a visual aid (MIN X0707), and has reconsidered our position on several promotional issues presented in these materials, pursuant to the provisions of 21 CFR §202.1(j)(4).

Specifically, APLB objects to the following promotional presentations and messages:

False or Otherwise Misleading Claims

General

1. The tagline "*Strength for Living*" is misleading because it implies that Procrit improves strength and may improve survival when these outcomes have not been demonstrated by adequate and well-controlled clinical studies.

2. The presentations are misleading because the patient models depicted are not representative of the general population of chemotherapy patients, who would appear weaker and have hair loss, among other side effects.

3. Claims or implications that Procrit treats weakness and fatigue, or that Procrit increases strength, are misleading. Procrit is indicated for the treatment of anemia in patients receiving chemotherapy for non-myeloid cancers. The presentations imply that Procrit would improve fatigue and weakness in any chemotherapy patient when, in fact, Procrit only has been shown to increase red blood cells in chemotherapy patients with anemia. Chemotherapy patients may have fatigue and weakness due to factors other than anemia. Thus, increasing red blood cells with Procrit would not necessarily improve a patient's condition of weakness and fatigue.

Ralph Smalling – Page 2

DTC Broadcast Advertisements

1. The claim "*Procrit is a natural way to regain red blood cells lost during chemotherapy*" is misleading because the term "natural" implies that the product is safer or more effective than other products or methods to increase red blood cells when this has not been demonstrated in adequate and well-controlled studies.

2. The broadcast advertisements are misleading because they fail to disclose that Procrit is an injectable product.

3. The claim that Procrit is "proven and safe" is misleading in DTC broadcast advertisements because consumers lack the background to understand that "proven [safety]" and "safe" are scientific terms-of-art relating to how relative benefits and risks are weighed. Consequently, consumers are likely to interpret the claim "proven and safe" as meaning that Procrit has minimal or no risks associated with its use; notwithstanding disclosure of the "major statement." In addition, the use of such a claim immediately preceding the "major statement" minimizes the subsequent risk disclosure.

Professional Print Advertisement
Visual Aid

1. The claims "Meaningful Survival", "Treatment Focuses on Prolonging Survival", "Anemia Impacts Outcomes" and "An independent prognostic factor for survival in multiple myeloma" are misleading because they imply that treatment with the product or correction of anemia improves or prolongs survival when, in fact, there was no difference in the survival data between Procrit and placebo-treated patients.

2. The claim "*Treatment Focuses on ...Managing Symptoms*" is misleading because it implies that the product will improve or manage symptoms associated with anemia when this has not been demonstrated by adequate and well-controlled clinical studies.

3. The claims that Procrit "*Makes all the Difference*" and "*Treatment Focuses on ... Maintaining Functional Abilities*" are misleading because they imply that the product will improve or maintain health related quality-of-life when this has not been demonstrated by adequate and well-controlled clinical studies with validated instruments designed to measure quality-of-life parameters.

4. The bar graph depicting the increase in hemoglobin levels (page 6 in the visual aid) is misleading in the absence of contextual information regarding the percentage of patients who responded to therapy with 1.8 g/dl increases from baseline.

Lack of Fair Balance

1. Promotional materials are lacking fair balance if they fail to provide important risk information. For example, the DTC advertisements fail to disclose that Procrit is contraindicated in patients with uncontrolled hypertension. Furthermore, the DTC advertisements, professional print advertisements, and visual aid fail to disclose that common side effects include fever, shortness of breath, paraesthesia and upper respiratory infection, in addition to diarrhea and edema. Moreover, the printed materials are lacking fair balance because the risk information is not provided with a prominence and readability that is reasonably comparable to the presentations regarding the effectiveness and benefits of Procrit.

2. In the broadcast advertisements, the statements "Procrit is safe and effective" and "Procrit is proven and safe" immediately preceding the "major statement" minimize and undermine the communication of the subsequent risk information.

3. The broadcast advertisement entitled, "Anthem" is lacking fair balance because the background audio interferes with and minimizes the risk information.

"Adequate Provision" Requirement Not Fulfilled

1. For these widely disseminated DTC broadcast advertisements, "Coping" magazine is not considered to have a range of distribution wide enough to reach the targeted audience (i.e., including "newsstand" availability for consumers seeking anonymity). Therefore, dissemination of the DTC print advertisement component in this magazine does not fulfill the "adequate provision" requirement.

2. The superimpositions of the print ad component and website component for partial fulfillment of the "adequate provision" requirement in the broadcast advertisements lack adequate prominence and readability.

Failure to Adequately Disclose Prescription Drug Status

In the DTC broadcast advertisements, the superimpositions regarding the prescription only status of the product lack adequate prominence and readability.

The above comments apply to Procrit promotional materials that contain the same or similar claims or presentations. Please note that the market research provided in your letter dated January 5, 2001, does not adequately address the promotional issues in question.

Please note that, whenever possible, DTC information should be communicated in consumer-friendly language. For example, the statements, "*Procrit is for patients with*

non-myeloid cancers" and "*It's for chemotherapy patients with non-myeloid cancers*" should be revised to be more understandable to the consumer (e.g., "forms of cancer that do not start in your bone marrow or certain types of cancers").

APLB recognizes that the above issues have not been addressed fully in discussions with OBI concerning the development of the DTC advertisements. Thus, APLB will provide you with a reasonable period of time to make necessary revisions to the Procrit promotional materials. Accordingly, revisions should be completed within 90 days of receipt of this letter, or at the next printing or taping of the affected materials, whichever comes first.

Within 10 days, please notify APLB in writing with your intent to comply with this request. Include a list of all promotional materials that have been discontinued, as well as a list of materials that will be revised within the specified time frame.

Your written response should be sent to the attention of Ms. Carole Broadnax at the following address:

Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
Advertising and Promotional Labeling Branch, HFM-602
1401 Rockville Pike
Rockville, MD 20852-1448

We remind you that only written communications are considered official.

Sincerely,

Mary A. Malarkey
Director
Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosure(s)

cc: Minnie Baylor-Henry, R.Ph., J.D.
Sr. Director, Regulatory Affairs
Advertising and Promotion Review
The R.W. Johnson Pharmaceutical Research Institute
Route 202, P.O. Box 300
Raritan, NJ 08869-0602

Ralph Smalling – Page 5

Firm name: Amgen Inc.

Letter type: Untitled

bcc:	HFM-602	C. Broadnax
	HFM-602	APLB Letter File
	HFM-602	APLB Complaint File
	HFM-99	DCC
	HFM-48	OCTMA
	HFM-610	DCM Clipboard
	HFM-610	M. Malarkey
	HFM-573	S. Litwin

History:
Prepared by: C. Broadnax: 8/27/01, 8/31/01, 9/5/01, 10/4/01, 10/19/01
Comments by: C. Miller: 8/30/01, 10/5/01
Comments by: T. Stifano: 9/4/01
Comments by: N. Ostrove: 9/14/01
Comments by: J. Hankin: 9/14/01, 12/17/01
Comments by: L. Stockbridge: 9/14/01, 12/17/01
Comments by: S. Litwin: 10/15/01, 10/19/01, 12/19/01
Finalized by: C. Broadnax: 12/20/01

File name: (P10201011, P10201025, P10827003, P10828003, P11001014, P11220001, P11220002, P111220003)
Address:Cbs\5055682\OC\APLB\APLB\broadnax\Procrit\Procrit anthem letter – final.doc

Concurrence box:

MailCode or Office	Name	Date
HFM-602	Broadnax	12/20/01
610	Malarkey	12/20/01

MailCode or Office	Name	Date

1/10/02

DT MR
ML
Seth

→ CBER's regulation of press releases

SR/DT - OCC looking @ letter so should help

DT - provide guidance to DDMAC + CBER

DT - fully protected → 1st Am speech
context matters
not commercial speech

DT - shouldn't start w/ press releases -
start w/ clear activity

→ readjustment in thinking
presumption - may not speak
presumption - you may speak
→ FDA must say what you do is wrong

DT - as long as company stays away from saying literally S+E
+ they describe it -
w/ adequate disclaimer } OK

Ralph Smalling
Vice President Regulatory/Medical Affa

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805-447-1000
Direct Dial [redacted]
Fax [redacted]

Mary A. Malarkey
Director
Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

JAN 25 2002
75528

Cc: Carol Broadnax + Attachments
Seth Ray, Esq. + Attachments

Dear Ms. Malarkey:

I am writing to you regarding the letter dated December 21, 2001 regarding several promotional materials distributed by Ortho Biotech Products, L.P. As you know, Ortho markets Procrit® (Epoetin alfa) through a product license agreement with Amgen. Ortho has drafted the following response to your letter and has asked Amgen to transmit it to you for your consideration:

We are in receipt of your letter dated December 21, 2001, issued under 21 CFR 202.1(j)(4), notifying us that the Food and Drug Administration (FDA) has changed its opinion regarding the status of several of the promotional pieces that were disseminated by Ortho Biotech Products, L.P. (OBP). Specifically, FDA referenced two direct-to-consumer (DTC) broadcast advertisements, two DTC print advertisements, a professional print advertisement, and a visual aid.[1] While we very much appreciate FDA's willingness to grant a reasonable period of time for the requested revisions to the cited pieces, we respectfully disagree with the stated justification and the regulatory bases for many of the requested changes. Accordingly, we ask that the agency reconsider its position, after carefully evaluating our response. In order to facilitate the review and closure of the issues, we are also including a request for a teleconference.

Allegedly False or Otherwise Misleading Claims

General

- *The tagline "Strength for Living" is misleading because it implies that Procrit improves strength and may improve survival when these outcomes have not been demonstrated by adequate and well-controlled clinical studies.*

Response:

It is unclear how FDA reached the conclusion that the intent of the tagline "Strength for Living" was to imply that Procrit improves strength and improves survival. Clearly, there is an improvement in the symptoms associated with anemia. This is clinically supportable and is the only meaning that should be attributed to the tagline. OBP's copy testing of this claim showed that most people recalled (63-71%) the phrase, with 56-72% stating that it meant "gives you strength or energy". It is worth noting that only 0-7% believed it meant "helps you live longer".

In order to understand FDA's perspective on this subject, it would be helpful if FDA would distinguish the "Strength for Living" tagline from similar claims in other currently running broadcast advertisements. These claims include,

[1] Broadcast Advertisements: *"Anthem"* (10/00) and *"Big Boy Bed" (8/01);* 2 DTC Print Ads: 08PCTC1317 (9/[illegible] Professional Print: 08PCTC1218 (2/01) and Visual Aid: 08PCTC1324 (9/01)

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"You can be stronger than diabetes" (Avandia®); "Why live this way another month" (Sarafem™); "Your life is waiting" (Paxil®); or "Life should take your breath away, not asthma" (Advair™). Likewise, similar messages appear in DTC print advertisements, including "Love life again" (Viagra®); "Down with your blood sugar. Up with your life" (Glucophage®); "Look, I have asthma, but I also have a life" (Singulair®); and "It's your life-fight for it" (Pravachol®). We would welcome some guidance regarding the outcomes study designs that were employed to support the above referenced claims that appear in many current broadcast and print advertisements.

- *The presentations are misleading because the patient models depicted are not representative of the general population of chemotherapy patients, who would appear weaker and have hair loss, among other side effects.*

Response:

We contend that there is no typical chemotherapy patient. Not all patients appear weak and not all have a total loss of hair. In fact, the incidence of alopecia reported in the labeling for several commonly prescribed chemotherapy agents reveals an incidence rate ranging from under 5% to rates as high as 87% *(See Attachment 1)*. Accordingly, the "typical" patient varies and cannot be typecast.

In furtherance of this position and given the importance of effective communication, particularly with cancer patients, we wish to share with FDA some research findings that we thought would be of interest. OBP's continuous tracking study results indicate that 83% of the chemotherapy patients identify with the people in the Procrit commercial and 93% identify with the situations.

OBP also conducted qualitative research (6 focus groups in 2 cities/3 per city). This research specifically probed the realism of the people in the Procrit commercial. The research overwhelmingly confirmed the quantitative tracking study; in that people found the commercial to be sensitive and believable in the situations portrayed. There appeared to be a desire to blend aspiration with reality. All chemotherapy patients emphasized the importance of maintaining a positive attitude characterized by a countenance that reflected that attitude (a smile, a hopeful expression).

In light of these research findings, we ask that FDA share with us its standard for evaluating the appropriateness of the models to be used in a broadcast advertisement. For example, are the very physically active models in the current Celebrex® broadcast advertisements or Dorothy Hamill in the Vioxx® DTC print advertisement typical of the general population of osteoarthritis patients? Likewise, is Peggy Fleming typical of a patient with hyperlipidemia or Lance Armstrong typical of a testicular cancer patient? We believe that it is clear that these individuals, including the celebrity spokespeople, represent models in aspirational advertising and, as such, the advertisements focus on the potential success, after being treated with the drug product. If we are correct in this presumption, we question why FDA is imposing a different standard on the portrayal of the typical cancer patient that is suffering from the anemia associated with cancer chemotherapy. This is particularly interesting in light of the depictions seen in promotional and educational pieces from the American Cancer Society, Coping magazine, a breast cancer support group, a Nolvadex® (tamoxifen citrate) print advertisement and Taxotere® (docetaxel) print advertisement *(See Attachment 2)*. You will note that the models in these pieces appear to be healthy and have full heads of hair.

Lastly, as FDA evaluates this issue, we wish to share with you that the model in our broadcast advertisement, *Big Boy Bed*, is in fact a cancer survivor. He started chemotherapy for colorectal cancer in December 1999 and continued therapy until October 2000. We are particularly proud to be associated with this fine gentleman.

- *Claims or implications that Procrit treats weakness and fatigue, or that Procrit increases strength, are misleading. Procrit is indicated for the treatment of anemia in patients receiving chemotherapy for non-myeloid cancers. The presentations imply that Procrit would improve fatigue and weakness in any chemotherapy patient when, in fact, Procrit only has been shown to increase red blood cells in chemotherapy patients with anemia. Chemotherapy patients may have fatigue and weakness due to factors other than anemia. Thus, increasing red blood cells with Procrit would not necessarily improve a patient's condition of weakness and fatigue.*

Response:

Anemia is a common complication of myelosuppressive chemotherapy. A considerable number of patients develop anemia during the course of chemotherapy. In fact, the overall incidence of chemotherapy-induced anemia is most likely much higher than previously recognized. Most published oncology trials focus on the higher grades of toxicity or the most severe toxic effects. In the case of anemia, grades 3 (serious or severe; 6.5-7.9 g/dL) and 4 (life threatening; <6.5 g/dL) are typically reported. The incidence of lower grades of anemia, such as grades 1 (10g/dL to normal limits) and 2 (8.0-10.0 g/dL) are under-reported (Groopman JE, et al. *J Natl Cancer Inst.* 1999; 91:1616-1634; Nowrousian MR. *Med Oncol.* 1998; 15(suppl 1): S19-S26) *(See Attachment 3).*

As stated in OBP's letter to FDA on January 5, 2001, we continue to believe that consumers do not clearly understand the correlation between their fatigue and the diagnosis of anemia. They view anemia as a laboratory value, but do not connect this laboratory value to their feelings of tiredness. In order to facilitate this understanding, OBP has consistently tied the symptoms of fatigue to the actual condition of anemia in all promotional pieces.

Therefore, today as always, we contend that fatigue is a cardinal symptom of chemotherapy-induced anemia and the relationship between anemia and fatigue is universally accepted *(See Attachment 4).* In a survey of cancer patients, fatigue was the primary complaint experienced during chemotherapy. Fatigue is a subjective sensation often described as a feeling of tiredness, weakness, lack of energy, exhaustion, lethargy, or malaise. In a large trial of 2,289 patients receiving chemotherapy, anemia significantly correlated with fatigue and its functional consequences. (Demetri D. *J Clin Oncol.* 1998; 16:3414-3415) *(See Attachment 4e).* In light of the overwhelming data, we believe that the correlation between cancer chemotherapy and anemia, as well as anemia and the symptom of fatigue are beyond question.

Regarding the practice of describing the symptoms associated with a disease state in promotional material, there are numerous examples, in many therapeutic areas, including, but not limited to, the SSRIs, Alzheimer's products, and gastrointestinal agents *(See Attachment 5).* We, therefore, question why FDA believes that when discussing anemia, it would be any less appropriate to discuss the symptoms associated with this often misdiagnosed condition, when there is probably an even greater need for education. We also find your request to discontinue the claims to be confusing. The cited pieces consistently and prominently state that Procrit is indicated for chemotherapy patients with anemia and that the product is only indicated for non-myeloid cancer.

DTC Broadcast Advertisements

- *The claim "Procrit is a natural way to regain red blood cells lost during chemotherapy" is misleading because the term "natural" implies that the product is safer or more effective than other products or methods to increase red blood cells when this has not been demonstrated in adequate and well-controlled studies.*

Response:

We disagree that the claim implies that the product is safer or more effective than other products or methods to increase red blood cells. The use of the word "natural" properly refers to the fact that epoetin alfa's mode of action is via a natural mechanism, stimulating erythropoiesis in an identical manner to endogenous erythropoietin. The molecule with the same amino acid sequence as the endogenous form accordingly enables red blood cells to be produced through a mechanism "existing in or caused by nature" (See Oxford Dictionary definition). The natural attribute of this treatment is in direct contrast with allogeneic blood transfusion that does not exist in nature. The use of the term natural is clearly non-comparative. Moreover, in fulfillment materials for DTC ads (see e.g., www.procrit.com/cancer/cancer_05.htm), we provide additional context to our use of the term "natural". For example, the materials describe the product as a "man-made version of the endogenous form". In no way are there claims that the product is naturally derived or that it has a comparative safety advantage due to its mode of action.

We ask that FDA help us to reconcile the difference between the use of the term natural in the Procrit broadcast advertisement as opposed to a similar claim in the Avandia broadcast and print advertisements. The Avandia advertisements state, "It helps my body use its own natural insulin more effectively....". Similarly, the print

advertisement for Enbrel states, "Because Enbrel is a protein similar to one your body produces naturally, it targets rheumatoid arthritis in a unique way."

- *The broadcast advertisements are misleading because they fail to disclose that Procrit is an injectable product.*

Response:

We disagree that the broadcast advertisements are misleading because they fail to mention that Procrit is an injectable. First, Procrit must be administered by a health care professional and, secondly, the Procrit advertisements target a patient population that clearly understands that most, if not all, of the usual and customary treatments are given by injection.

Your allegation is particularly interesting because a survey of the broadcast advertisements that aired during the calendar year 2001 reveals a clear inconsistency in how various companies have handled the description of dosage forms in their TV advertisements. This ranges from no specific mention to many other variations. Nevertheless, we agree to include the word, injectable, at the first display of the brand and generic name in future broadcast advertisements. This modification fully satisfies the letter and the spirit of the law and is consistent with many of the currently running advertisements for other prescription drug products.

- *The claim that Procrit is "proven and safe" is misleading in DTC broadcast advertisements because consumers lack the background to understand that "proven [safety]" and "safe" are scientific terms-of-art relating to how relative benefits and risks are weighed. Consequently, consumers are likely to interpret the claim "proven and safe" as meaning that Procrit has minimal or no risks associated with its use; notwithstanding disclosure of the "major statement." In addition, the use of such a claim immediately preceding the "major statement" minimizes the subsequent risk disclosure.*

Response:

We respectfully request that FDA share the objective data it relied upon to conclude that consumers, particularly cancer patients, "lack the background" to understand the intended meaning of proven and safe. It is clearly recognized that cancer patients are actively involved in seeking as much information as possible about their condition. FDA recognized the information seeking needs of this population and, several years ago, advocated for cancer patients to have access to the Clinical Trials Updates on the National Institutes of Health (NIH) website. The information on NIH's website is clearly more technical than any information that may appear in a 60-second broadcast advertisement for Procrit.

It also is unclear whether FDA believes that cancer patients will have difficulty understanding the word proven or the word safe. Since safe is a word that is likely to be understood by most grade school students, we must conclude that proven is of greatest concern. We question FDA's presumption that consumers are unable to understand the meaning of the word, proven, in the context of a prescription drug advertisement. The claim of "proven" or "clinically proven" appears in current advertisements, broadcast and/or print, for Actonel™, Advair™, Aldara,™ Glucovance®, Detrol ®LA, Fosamax®, Nexium®, Plavix®, Pravachol®, Wellbutrin®, Zocor®, and Zyrtec® *(See Attachment 6)*. It should be noted that in the aforementioned examples from the broadcast medium, the claim of "proven" appears before the "major statement". Since it appears that FDA did not believe there would be consumer confusion in these advertisements, it would be helpful to understand what FDA relied upon in distinguishing the use of the claim of "proven" in the referenced Procrit advertisement from its use in other currently running broadcast and print advertisements.

Lastly, we contend that the claim of "proven and safe" is synonymous to the claim of "safe and effective", or for that matter with the term "approved". In fact, your letter states that proven and safe is a "term-of-art" pertaining to how relative benefits and risks are weighed. This is an accurate description of FDA's standard for determining that a

drug is safe and effective. In this regard, we remind you that the 1997 Food and Drug Administration Modernization Act specifically deleted Section 301(l) from the Federal Food, Drug, and Cosmetic Act.[2]

Professional Print Advertisement
Visual Aid

- *The claims "Meaningful Survival", "Treatment Focuses on Prolonged Survival", "Anemia Impacts Outcomes" and "An independent prognostic factor for survival in multiple myeloma" are misleading because they imply that treatment with the product or correction of anemia improves or prolongs survival when, in fact, there was no difference in the survival data between Procrit and placebo-treated patients.*

Response:

In the visual aid, the following statements "Treatment Focuses on Prolonging Survival", "Anemia Impacts Outcomes" and "An independent prognostic factor for survival in multiple myeloma" are not related to PROCRIT therapy and are intended to be separate and distinct messages that refer to anticancer therapy, such as chemotherapy. These statements are physically separated through the use of tabbed sections (tabs labeled NHL and MM) from the information on PROCRIT treatment (tabs labeled AIM and Reimbursement).

"Meaningful Survival" is not intended to convey that PROCRIT improves patient survival. It is chemotherapy that improves survival. Newer chemotherapy treatment options have improved response rates and may extend survival (Crown J. *Semin Oncol.* 1998; 25(suppl 12): 12-17; Shepherd FA. *Semin Oncol.* 1999; 26(suppl 4): 3-11). Many of these new chemotherapy regimens are myelosuppressive and are associated with a high and cumulative incidence of anemia. A comprehensive review article by Groopman and Itri on the incidence of chemotherapy-induced anemia provides support for this statement (*J Natl Cancer Inst.* 1999; 91:1616-1634). The toxicity of chemotherapy-induced anemia and declining hemoglobin levels can make any gains in survival less meaningful to the patient. In fact, in a study of lung cancer patients previously treated with cisplatin, the majority of patients (68%) chose to receive chemotherapy if it substantially reduced symptoms without prolonging life, while only 22% chose chemotherapy for a 3-month survival benefit (Silvestri G. *BMJ.* 1998; 317:771-775). The phrase "Meaningful Survival", as defined in *Handbook of Cancer Chemotherapy* by Roland T. Skeel, is an aim of therapy that addresses the need to balance chemotherapy-associated survival gains with chemotherapy-associated treatment toxicities. Specifically, "For advanced disease (in this case, breast cancer), the aim is usually to reduce the tumor burden temporarily and the resultant disability in order to alleviate the patient's symptoms, improve performance, and prolong meaningful survival." *(See Attachment 7).*

In the visual aid, "Treatment Focuses on Prolonging Survival" specifically refers to the anticancer therapies listed in the chart such as chemotherapy and radiation that are used to treat Non-Hodgkin's Lymphoma. The goal of these treatment options is to prolong survival, "since many patients with NHL can be successfully treated and continue to have an excellent quality of life, it is important to optimize the therapeutic options available to these patients:". (Vose JM. *Semin Oncol.* 1998;25:483-491. Reference 1 in the visual aid). The statement, "Treatment Focuses on Prolonging Survival" does not refer to PROCRIT. In fact, the name PROCRIT or Epoetin alfa does not appear on this spread *(See Attachment 8).*

In the visual aid, "Anemia Impacts Outcomes" is supported by the 5 cited references. Outcomes refer to the impact of symptoms of anemia, functional capacity, and survival. From reference 6 of the visual aid, "Anemia results in important symptoms for the patient. Common symptoms include fatigue, breathlessness, swollen feet, chest pain, and loss of mental acuity." (Littlewood TJ. *Hematol Oncol.* 2001;19:19-30). Reference 10 of the visual aid is entitled, "The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: A New Tool for the Assessment of Outcomes in Cancer Anemia and Fatigue.". When patients were divided into 2 groups by hemoglobin levels, patients with hemoglobin levels >12 g/dL reported fewer anemia symptoms such as fatigue and "better physical well-being" and "better functional well-being" (Cella D. *Seminars in Hematol.* 1997; 34(suppl 2): 13-19). Lastly, reference 8 of the visual aid, entitled, "Anemia As An Independent Prognostic Factor For Survival In Patients With

[2] Section 301(l) of the Federal Food, Drug, and Cosmetic Act stated, "The following acts and the causing thereof are hereby prohibited…The using, on the labeling of any drug or device, or any advertising relating to such drug or device, of any representation or suggestion that approval of an application with respect to such drug or device is in effect…."

Cancer" is a systematic, quantitative review examining the correlation between anemia and survival in cancer patients. This author concludes that "anemia is associated with shorter survival times for patients with lung carcinoma, cervicouterine carcinoma, head and neck carcinoma, prostate carcinoma, lymphoma, and multiple myeloma." (Caro JJ, et al. *Cancer.* 2001; 91:2214-2221) *(See Attachment 9).*

The statement, "Anemia Impacts Outcomes" refers to the impact of anemia as a clinical condition. It does not refer to the correction of anemia with PROCRIT. Once again, the name PROCRIT or Epoetin alfa does not appear on this spread.

In the visual aid, anemia is "An independent prognostic factor for survival in multiple myeloma" is supported by the author's conclusion that anemia is associated with shorter survival times for patients with many tumor types including multiple myeloma. The statement, "An independent prognostic factor for survival in multiple myeloma" does not refer to PROCRIT. In fact, the name PROCRIT or Epoetin alfa does not appear on this spread.

- *The claim "Treatment Focuses on...Managing Symptoms" is misleading because it implies that the product will improve or manage symptoms associated with anemia when this has not been demonstrated by adequate and well-controlled clinical studies.*

Response:

In the visual aid, this statement specifically refers to the anticancer therapies listed in the chart such as chemotherapy and bone marrow transplant. As stated in reference 18 of the visual aid, "...appropriate goals of treatment [with chemotherapy] for multiple myeloma today are to induce long term survival, assure prolonged relief from symptoms, and protect patient's ability to function for as long as possible." (Oken MM, et al. *Cancer.* 1997; 79:1561-1567) *(See Attachment 10).* The statement "Treatment Focuses on ... Managing Symptoms" does not refer to PROCRIT. In fact, the name PROCRIT or Epoetin alfa does not appear on this spread.

- *The claims that Procrit "Makes all the Difference" and "Treatment Focuses on...Maintaining Functional Abilities" are misleading because they imply that the product will improve or maintain health related quality-of-life when this has not been demonstrated by adequate and well-controlled clinical studies with validated instruments designed to measure quality-of-life parameters.*

Response:

In the professional print ad and the visual aid, "Makes all the Difference" refers to the treatment-related goal of "Meaningful Survival." Meaningful Survival, as previously stated, is a common goal of cancer therapy (DeVita VT. *Cancer: Principles and Practices of Oncology*; Skeel RT. *Handbook of Cancer Chemotherapy*) *(See Attachment 11).* Part one of this treatment-related goal is improving survival through anticancer therapy (i.e., chemotherapy). Part two refers to the need to help make this survival "meaningful by managing the toxicities (i.e., anemia) of anticancer therapy. The two-fold nature of "Meaningful Survival" is expressed by the following two sentences that appear on the professional print ad and the visual aid: "Newer chemotherapy treatment options have improved response rates and may extend survival. Help provide meaningful survival during chemotherapy by treating anemia.". Through the inclusion of these two sentences, it is clear that extending survival is attributed to chemotherapy. The benefit of PROCRIT is in managing anemia: a key toxicity of chemotherapy.

- *The bar graph depicting the increase in hemoglobin levels (page 6 in the visual aid) is misleading in the absence of contextual information regarding the percentage of patients who responded to therapy with 1.8g/dl increases from baseline.*

Response:

The two bar graphs represent the *mean* increases in hemoglobin from baseline to final measurement for NHL and MM patients. For NHL patients (n=390), the mean increase was 1.8g/dL (SD 2.4); for MM patients (n=299), the mean increase was 1.8g/dL (SD 2.0). Both mean increases were statistically significant (P<.0001). These data were derived from two (1 for each tumor type) pooled retrospective, post hoc subset analyses of two large nonrandomized, multicenter trials of up to 4 months of PROCRIT therapy in patients receiving chemotherapy.

While we believe the current version of the bar graph is clear, we will agree to include the above additional contextual information, if this presentation is made in the future.

Lack of Fair Balance

- *Promotional materials are lacking fair balance if they fail to provide important risk information. For example, the DTC advertisements fail to disclose that Procrit is contraindicated in patients with uncontrolled hypertension. Furthermore, the DTC advertisements, professional print advertisements, and visual aid fail to disclose that common side effects include fever, shortness of breath, paraesthesis and upper respiratory infection, in addition to diarrhea and edema. Moreover, the printed materials are lacking fair balance because the risk information is not provided with a prominence and readability that is reasonably comparable to the presentation regarding the effectiveness and benefits of Procrit.*

Response:

In addition to the cited language, there is language in the *Precautions* section of the labeling that states "Hypertension, associated with a significant increase in hematocrit, has been noted rarely in cancer patients treated with Procrit. Nevertheless, blood pressure in patients treated with Procrit should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease."

There are numerous examples of broadcast advertisements where contraindications or precautions are not mentioned in the advertisement. For example, the Nexium™ broadcast advertisement mentions no contraindications and the Imitrex® broadcast advertisement mentions some, but not all of the contraindications. Likewise, Celebrex® labeling has a precaution regarding patients with fluid retention, hypertension, or heart failure. However, this information is not included in the Celebrex DTC advertisements.

We strongly believe that the information regarding hypertension that appears in the Procrit labeling is more relevant to and appropriate for the healthcare provider. Blood pressure monitoring is a routine part of the overall care for chemotherapy patients. Therefore, we have included the disclosure in all of our professional pieces.

Regarding the inclusion of additional side effect information, it is unclear what standard FDA employed in determining which side effects were appropriate for inclusion in the referenced pieces. FDA has not issued a guidance or regulations for determining what information should or should not be included when reporting side effects in a promotional context. There are a number of inconsistencies and the data reported varies considerably between products. For example, Allegra® reports upper respiratory tract infections despite there being little difference vs. placebo (3.2% for Allegra vs. 3.1% for placebo). On the otherhand, Zyrtec®, which is in the same category, lists drowsiness, fatigue and dry mouth, but not dizziness, despite the fact that it was reported at 2.0% Zyrtec vs. 1.2% placebo.

In light of these clear inconsistencies, we determined that the appropriate method for reporting such data should be to look at the side effects that were statistically different from placebo and to include such data in our promotional material.

If FDA has determined a standard for the reporting of side effect information in advertisements or promotional labeling, we would welcome the opportunity to provide comments in response to the publishing of a draft guidance in the *Federal Register*.

- *In the broadcast advertisement, the statement "Procrit is safe and effective" and "Procrit is proven and safe" immediately preceding the "major statement" minimize and undermine the communication of the subsequent risk information.*

See response above under *DTC Broadcast*

- *The broadcast advertisement entitled, "Anthem" is lacking fair balance because the background audio interferes with and minimizes the risk information.*

The broadcast advertisement entitled "Anthem" first aired August 31, 2000 and ran until June 2001 at which time it was discontinued.

"Adequate Provision" Requirement Not Fulfilled

- *For these widely disseminated DTC broadcast advertisements, "Coping" magazine is not considered to have a range of distribution wide enough to reach the targeted audience (i.e., including "newsstand" availability for consumers seeking anonymity). Therefore, dissemination of the DTC print advertisement component in this magazine does not fulfill the "adequate provision" requirement.*

Response:

It is important to distinguish the "Guidance for Industry-Consumer-Directed Broadcast Advertisements" from a binding rule. Since a guidance is not binding and, since FDA has stated that there are other acceptable means for complying with the law, we question whether newsstand distribution is the only means for satisfying the "adequate provision' requirement. Further, in light of the fact that FDA has not provided the regulated industry with any objective standards for determining what constitutes an acceptable "reach," we determined that it was more important to reach 80,000 targeted cancer patients through a magazine, such as Coping, than to focus on a more general audience. However, given the fact that our print advertisements also appear in more general audience magazines, in the future, we will reference one of these publications.

- *The superimposition of the print ad component and website component for partial fulfillment of the "adequate provision" requirement in the broadcast advertisements lack adequate prominence and readability.*

Response:

OBP's objective is to have the targeted patient population clearly see the references to the print advertisement and the URL address. The utilization of additional sources of information can only serve to further educate the patient about cancer and the appropriate use of Procrit. We are aware of the fact that approximately one-third of chemotherapy patients use the Internet for health related information. OBP's research indicates that 60% of the respondents said they would be very or somewhat likely to look on the Internet to learn more about Procrit after having seen OBP's commercial. It should be noted that the norm for this type of testing is 30%. Additionally, OBP participated in a large industry benchmark study of drug web site users. Results indicate that 25% of Procrit site users located the site by typing the web address they saw on television. Notwithstanding this high rate of recall and associated action, we will endeavor to make the reference to the print component and the URL address even more prominent in future broadcast advertisements.

Failure to Adequately Disclose Prescription Drug Status

- *In the DTC broadcast advertisements, the superimposition regarding the prescription only status of the product lack adequate prominence and readability.*

Response:

A survey of the current broadcast advertisements reveals that the reference to the prescription status in the Procrit advertisement is similar to the reference in most of the other advertisements. In the advertisement, *Big Boy Bed*, the claim, "by prescription" remained on the screen for 3.04 seconds as compared to an average of 3 seconds in other broadcast advertisements.

We recognize that FDA has determined that the market research data we provided on January 5, 2001, do not adequately address the promotional issues in question. However, it is disappointing that in almost a year, FDA did

not notify us with questions about the submitted data. We have additional data and would have welcomed the opportunity to provide FDA with additional information, if such had been requested. In this regard, we have enclosed some of these data. We believe the information provides support for our claims. Should FDA determine that there is a need for additional data, we ask that FDA notify us, so we can work together in a collaborative manner to resolve any issues.

Regarding FDA's suggestion that DTC information be conveyed in consumer-friendly language, we are in complete agreement. In future broadcast advertisements, we will revise the claim to read, "Procrit... is for patients with most types of cancer." Since over 90% of the cancers are clinically characterized as non-myeloid, this is a truthful claim and satisfies the need to communicate in consumer-friendly language.

We would appreciate FDA's careful review of our response, along with the accompanying data. OBP is anxious to resolve the issues that were cited in your December 21, 2001 letter, as well as any outstanding issues from your letter of June 30, 2000 *(See Attachment 12)*. In order to facilitate closure of these issues, we have attached a request for a teleconference *(See Attachment 13)*. In preparation for this teleconference, we would appreciate it if FDA would share the data it relied upon to reach many of the conclusions stated in the letter. We believe this exchange of information will ensure a more meaningful dialogue.

Should you have any questions or require further information, please contact either Becky Cleavenger or myself at [redacted] or [redacted] respectively, or by FAX at [redacted]

Sincerely,

Ralph Smalling
Vice President,
Regulatory Affairs

2002-0122_BC_GC_OrthoResponsetoChangeOp ltr

ATTACHMENT 1	Incidence of Alopecia by Chemotherapy Agent
ATTACHMENT 2	ADVERTISEMENTS - Patient Models
ATTACHMENT 3	Reference List for Chemotherapy-Induced Anemia
ATTACHMENT 4	Reference List for *Fatigue Caused by Chemotherapy-Induced Anemia*
ATTACHMENT 5	PRINT ADS describing Symptoms associated with a Disease
ATTACHMENT 6	PRINT ADS with the claim *Proof* or *Proven*
ATTACHMENT 7	List of References for *"Meaningful Survival"* Response
ATTACHMENT 8	*Current Approaches to the Management of Non-Hodgkins Lymphoma*
ATTACHMENT 9	List of References for *"Anemia Impacts Outcomes"* Response
ATTACHMENT 10	*Comparison of Melphalan and Prednisone with Vincristine, Carmustine, Melphalan, Cyclophosphamide, and Prednisone in the Treatment of Multiple Myeloma*
ATTACHMENT 11	CANCER Principles & Practice of Oncology
ATTACHMENT 12	FDA and AMGEN/OBI Letters
ATTACHMENT 13	Request for Teleconference Meeting between Amgen/OBP and FDA

Vice President Regulatory/Medical Affai

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805: 447.1000
Direct Dial
Fax

February 12, 2002

Mary A. Malarkey, Director
Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

RECEIVED
FEB 13 2002
BA# 77391
CBER/DCC

Cc: Carol Broadnax
Seth Ray, Esq. OCC

Dear Ms. Malarkey:

Ortho markets Procrit® (Epoetin alfa) through a product license agreement with Amgen. Ortho has asked Amgen to transmit the following for your consideration:

Reference is made to our letter dated January 22, 2002, in response to your letter dated December 21, 2001. Your letter alleged that certain claims that appear or have appeared in some of the Ortho Biotech Products, L.P.' (OBP) promotional materials for Procrit are false or otherwise misleading. You requested that OBP revise all affected promotional material within 90 days after receipt of your letter, or at the next printing or taping of the material, whichever comes first.

We are writing to request that the Food and Drug Administration (FDA) reconsider the 90-day timeline stated in its December 21, 2001 letter. We ask that you grant this request for the following reasons:

1. The 90 day period for revisions is not required by the regulation at 21 CFR 202.1(j)(4)[1]. Rather, the regulation specifies that the advertiser will be granted a reasonable period of time. In this case, 90 days is not reasonable. As a result of contractual obligations associated with the production of these materials, it would cost OBP approximately $10 million dollars to meet a 90 day deadline. We request that we be permitted to discuss with the Agency what a reasonable period of time would be;

2. OBP's response letter indicated a clear disagreement with many of the allegations that FDA made and, therefore, a request for a meeting was included in our response. OBP requested this meeting in order to have a discussion with FDA regarding the bases for the agency's allegations. We are awaiting FDA's response to this meeting request.

After carefully considering the above stated concerns, we are once again asking that FDA expeditiously grant our request for a meeting. OBP believes that a meaningful dialogue will provide an opportunity for FDA to review with OBP the data it relied upon in determining that the referenced promotional pieces were false or otherwise misleading and permit OBP to further explain the data it relied upon to support its claims. At the end of the discussion, it is our goal to reach final resolution on these issues.

[1] 21 CFR 202.1(j)(4) states "... If the advertiser is notified that the submitted advertisement is not in violation and, at some subsequent time, the Food and Drug Administration changes its opinion, the advertiser will be so notified and will be given a reasonable time *(emphasis added)* for correction before any regulatory action is taken under this section...."

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We appreciate your consideration of this request. We will telephone Carole Broadnax or you on February 13, 2002, to ascertain your willingness to consider, not only our meeting request, but also our request for an extension of the 90-day revision period.

Should you have any questions or require further information, please contact either Becky Cleavenger or myself at [redacted] or [redacted] respectively, or by FAX at [redacted]

Sincerely,

Ralph Smalling
Vice President,
Regulatory Affairs

2002-0212_BC_GC_OrthoResponsetoChangeOp ltr

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
Advertising and Promotional Labeling Branch

REVIEW MEMORANDUM

Product Name:	epoetin alfa
Brand Name:	Procrit
Manufacturer:	Amgen Inc.
Distributor:	Ortho Biotech Products, L.P. (OBP)
Description:	Amgen/OBP undated response letter (received January 25, 2002) to CBER's December 21, 2001 advisory letter

Background:

This review addresses the Center for Biologics Evaluation and Research (CBER) and the Division of Drug Marketing Advertising and Communications (DDMAC), Center for Drug Evaluation and Research (CDER) assessment of Amgen/OBP's January 2002 response letter to CBER's December 2001 advisory letter and OBP' s specific questions provided in Amgen's March 1, 2002 correspondence.

CBER met internally on February 28, 2002, and with DDMAC by teleconference call on March 14, 2002, to discuss Amgen's response letter.

GENERAL APPROACH:

DDMAC's position with OBP's drug advertisement examples
- The drug advertisements used as examples are not comparing the same types of things.
- Notify the Office of the Chief Counsel (OCC) that the drug advertisements provided as examples are not relevant.

DDMAC believes that CBER and CDER are consistent and that CBER's arguments are strong and we should stand by our position.

CBER's reconsideration based on review of arguments presented by OBP
- Refer to review discussion below.

Research to support agency's objections
- DDMAC has access to research and expert opinion.

AMGEN/OBP RESPONSE LETTER:

False or Otherwise Misleading Claims

General

1. **CBER objection summary:** "Strength for Living" tagline is misleading. It implies that Procrit improves strength and may improve survival.

OBP response summary: There is improvement in the symptoms associated with anemia. This is clinically supportable and is the only meaning that should be attributed to the tagline. OBP copying testing showed that most people (56%-72%) stated that the tagline means " gives you strength or energy." Only 0-7% believed it means " helps you live longer." OBP wants FDA to distinguish the tagline from similar claims in other currently running broadcast advertisements and would welcome outcomes study designs employed to support the claims in the current broadcast and print advertisements.

CBER response: Even OBP agrees with CBER by admitting the tagline means gives you strength or energy. There is no data to support the increase in strength claim. The living claim goes beyond increasing strength.

DDMAC response: DDMAC thinks CBER has a strong argument based on the fact that there is no data to support improvement in strength. Procrit does not improve strength. DDMAC provided their perspective regarding similar claims in other currently running broadcast advertisements; however, the following information must not be shared with Amgen/OBP. DDMAC is preparing an objection for the Viagra claim "Love life again" and the claim "Equipped for Living" for a Parkinson's drug.

The other drugs with similar claims have been shown to do what they are saying. For example, DDMAC allowed the Paxil claim, " Your life is waiting" after discussion. The reason is because the product is for social-anxiety disorder. Part of the indication is to get the patient out of the house. It is indication specific.

OCC response summary: OCC agrees that the " Strength for Living" tagline is misleading in terms of improvement in strength; however, they have a difficult time seeing how the living claim relates to improvement of survival.

2. **CBER objection summary:** Patient models are not representative of the general population of chemotherapy patient who would appear weaker and have hair loss.

OBP response summary: There is no typical chemotherapy patient, they vary and cannot be typecast. OBP's research showed that cancer patients found the people portrayed in the Procrit commercials to be sensitive and believable in the situation portrayed. OBP requests that FDA share with them our standard for evaluating the appropriateness of models used in a broadcast advertisement. OBP provides examples of very physically active models (Hamill, Fleming, Armstrong) in current drug broadcast advertisements. OBP questions why FDA is imposing a different standard for the portrayal of a typical cancer patient suffering from anemia associated with cancer chemotherapy in light of depictions seen in promotional and educational pieces from the American Cancer society, Coping magazine, a breast cancer support group and two cancer drug print advertisements. The model in the Big Boy Bed broadcast advertisement is a cancer survivor.

CBER response: The fine gentleman in the Big Boy Bed direct to consumer broadcast and print advertisements is acceptable since he is a cancer survivor. CBER's objection related more to the models in the Anthem broadcast and print advertisements. The " Anthem" broadcast advertisement has been discontinued according to OBP. What about the disposition of the print advertisements?

DDMAC response: DDMAC has objected in the past to cancer patient models. In March 2001, DDMAC issued a letter to Bristol-Myers Squibb for Ifex (ifosfamide) for a cancer patient who looked healthy. This letter stated, "*In addition, these claims combined with the pictoral representations of a very healthy-looking patient are misleading. The patient is not representative of a patient population that has already undergone first and second line chemotherapy and is now receiving third line chemotherapy containing a drug with a boxed warning of severe CNS toxicity, including coma, as well as significant side effects such as moderate to severe myelosuppression (50%), alopecia (83%), nausea-vomiting (58%), and hematuria (46%).*"
In April 2001, DDMAC issued a letter to Abbott Laboratories regarding promotional activities for drugs used in the treatment of human immunodeficiency virus (HIV) infection. This letter stated, "*DDMAC has also noted that some DTC materials and activities for HIV drug utilize images that are not representative of patients with HIV infection. Examples of such images range from robust*

individuals engaged in strenuous physical activity to healthy-looking individuals giving testimonials of a specific drug's benefit. However, not all individuals have a response to ARV therapy; in fact, some patients will still have disease progression despite ARV therapy. Furthermore, some images minimize the significant side effects profile associated with HIV drugs, including metabolic changes such as fat redistribution or facial wasting. Therefore, images that are not generally representative of patients with HIV infection are misleading because they imply greater efficacy than demonstrated by substantial evidence or minimize the risks associated with HIV drugs."

DDMAC thinks the fine gentleman in the Procrit advertisement is OK. Peggy Fleming is typical of a patient with hyperlipidemia. Dorothy Hamill is now typical of an osteoarthritis patient. She is in a lot of pain according to a Reader Digest article. She was on Larry King live and overstated the efficacy of Vioxx and Merck did a corrected commercial. The Vioxx advertisement is a poor example. The Lance Armstrong advertisement is a help-seeking ad, which FDA does not regulate.

OCC response summary: There is no definitive answer for this. Patient models have to be looked at on a case-by-case basis dependent on the product. Advise OBP to provide additional contextual information about the patient in future promotional material (for example, state that the patient did at one time have the products indicated disease state). This comment applies more to the discontinued Anthem broadcast advertisement than to the current Big Boy Bed broadcast advertisement.

3. **CBER objection summary:** Claims or implications that Procrit treats weakness and fatigue, or that Procrit increases strength, are misleading. The presentations imply that Procrit would improve fatigue and weakness in any chemotherapy patient when, in fact, Procrit only has been shown to increase red blood cells in chemotherapy patients with anemia. Chemotherapy patients may have fatigue and weakness due to factors other than anemia.

   OBP response summary: OBP continues to believe that consumers do not clearly understand the correlation between their fatigue and the diagnosis of anemia. In order to facilitate this understanding OBP has consistently tied the symptoms of fatigue to the actual condition of anemia in all promotional pieces and they contend that fatigue is a cardinal symptom of chemotherapy-induced anemia and the relationship between anemia and fatigue is universally accepted. OBP then refers the reader to attachment 4, which contains five references, which mostly discuss quality of life and quality of life instruments that relate hemoglobin, and hematocrit levels to improved quality of life. Three of the five references have some association with OBP. For example with the Demetri reference, the study was supported by a grant from Ortho Biotech Inc. and the author serves as a consultant to Ortho Biotech. OBP also cites examples of drug promotional materials that describe the symptoms associated with a disease state. OBP claims that the pieces cited in CBER's letter consistently and prominently state that Procrit is indicated for chemotherapy patients with anemia and that the product is only indicated for non-myeloid cancer.

   CBER response: OBP needs to concentrate on the implication that Procrit would improve the anemia in patients receiving chemotherapy for non-myeloid cancers and not just for the treatment of any anemic patient. This information needs to be framed differently in the advertisements. The cited pieces have intervening text between the initial discussion of chemotherapy and anemia and the later statement that Procrit is for patients with non-myeloid cancers.

   DDMAC response: Inferences are drawn although there is no guidance on this issue.

   OCC response summary: OCC agreed with CBER's and DDMAC's response.

DTC Broadcast Advertisements

1. **CBER objection:** The claim "*Procrit is a natural way to regain red blood cells lost during chemotherapy*" is misleading because the term "natural" implies that the product is safer or more effective than other products or methods to increase red blood cells when this has not been demonstrated in adequate and well-controlled studies.

OBP response summary: The use of the word "natural" properly refers to the fact that epoetin alfa's mode of action is via a natural mechanism, stimulating erythropoiesis in an identical manner to endogenous erythropietin. In fulfillment materials for DTC ads (OBP refers to the Procrit Internet site), OBP provides additional context to our use of the term "natural". For example, the materials describe the product as a "man-made version of the endogenous form". OBP requests that FDA help them to reconcile the difference between the use of the term natural in the Procrit broadcast advertisement as opposed to similar claims in the Avandia and Enbrel advertisements.

CBER response: OBP should bring out the additional context in their advertisements (e.g. that describe the product as a "man-made version of the endogenous form" of erythropoietin). The Avandia and Enbrel advertisements have nothing to do with CBER's position. The Enbrel example is in context. Enbrel is a protein similar to one the body produces naturally, which is different from saying that Enbrel is natural.

DDMAC response: Avandia does help the body use its own natural insulin more effectively which is different from saying Avandia is natural. DDMAC thinks CBER is on solid ground with our position. Procrit is an injection, which is not natural. Consumer's associate natural with dietary or herbal supplements. DDMAC will fax an article from the Drug Information Journal.

OCC response summary: OCC agreed with CBER's and DDMAC's response.

2. **CBER objection summary:** Failure to disclose that Procrit is an injectable product.

   OBP response summary: OBP disagrees with CBER's objection, however, OBP agrees to include the word, injectable, at the first display of the brand and generic name in future broadcast advertisements.

   CBER response: OBP's response is acceptable.

3. **CBER objection:** The claim that Procrit is "proven and safe" is misleading because consumers lack the background to understand that "proven [safety]" and "safe" are scientific terms-of-art relating to how relative benefits and risks are weighed. Consequently, consumers are likely to interpret the claim "proven and safe" as meaning that Procrit has minimal or no risks associated with its use; notwithstanding disclosure of the "major statement." In addition, the use of such a claim immediately preceding the "major statement" minimizes the subsequent risk disclosure.

   OBP response summary: OBP requests that the FDA share the objective data we relied upon to conclude that consumers, particularly cancer patients, "lack the background" to understand the intended meaning of proven and safe. It is unclear whether FDA believes that cancer patients will have difficulty understanding the word proven or the word safe. Since safe is a word that is likely to be understood, OBP concludes that proven is of greatest concern. OBP questions FDA's presumption that consumers are unable to understand the meaning of the word, proven, in the context of a prescription drug advertisement (examples provided where the claim "proven" appears before the "major statement".) OBP contends that the claim of "proven and safe" is synonymous with the claim of "safe and effective" or with the term "approved".

   CBER response: The product is "proven and safe" otherwise we would not have approved it.

   DDMAC response: This is not consistent with Janet Woodcock's (CDER Center Director) position. (re: risk information should not allow anyone to say a product is "safe" in the context of the relative benefits and risks). DDMAC is basing their opinion on expert opinion from FDA social scientists. The agency is willing to look at Ortho's data. The literature regarding "framing effects" is extensive. Proven effective is fine. Safe is a different issue.

   OCC response summary: OCC is not certain that CBER's objection is defensible. We may have a hard time arguing against proven and safe in context with risk information. We may not be on strong

grounds to object to placement (in reference to framing effects), however, without proper context safe may be an issue and should be fixed with context.

Professional Print Advertisement
Visual Aid

2 pieces
1 copy
1. translate
2. to Brad
Lou

1. **CBER objection:** The claims "*Meaningful Survival*", "*Treatment Focuses on Prolonging Survival*", "*Anemia Impacts Outcomes*" and "*An independent prognostic factor for survival in multiple myeloma*" are misleading because they imply that treatment with the product or correction of anemia improves or prolongs survival when, in fact, there was no difference in the survival data between Procrit and placebo-treated patients.

OBP response summary: "Meaningful Survival" is not intended to convey that Procrit improves survival. It is chemotherapy that improves survival.

In the visual aid, the statements "*Treatment Focuses on Prolonging Survival*", "*Anemia Impacts Outcomes*" and "*An independent prognostic factor for survival in multiple myeloma*" are not related to Procrit therapy and are intended to be separate and distinct messages that refer to anticancer therapy, such as chemotherapy. These statements are physically separated through the use of tabbed sectons (tabs labeled NHL and MM) from the Procrit information treatment tabs (tabs labeled AIM and Reimbursement). The name Procrit or Epoetin alfa does not appear on the spreads for these statements.

CBER response: The visual aid needs to be revised even though some of the information contained in the aid is not specific to Procrit. "Meaningful Survival" are the two largest words on the front and back covers of the visual aid and in the professional print ad in association with the Procrit tagline at the bottom of both pages of the visual aid and at the bottom of the print ad. In addition, the statements, especially the bolded statement, on the front cover of the visual aid and in the professional print advertisement, "Newer chemotherapy treatment options have improved response rates and may extend survival. **Help provide *meaningful survival* during chemotherapy by treating anemia with PROCRIT."** misleadingly implies that Procrit therapy or correction of anemia will improve or prolong survival.

DDMAC response: Since the Procrit tagline is in the same piece, but not on the same page, the information contained in the visual aid is still associated with Procrit. A disclaimer is needed for product discussion.

OCC/CBER response summary: OCC agreed with CBER's and DDMAC's response. OCC will support us on this. It is clear that Procrit does not improve survival. The professional print advertisement may have to be discontinued since it may not be as easily revised as the visual aid. This response also applies to item #'s 2 and 3 below.

2. **CBER objection:** The claim "*Treatment Focuses on ...Managing Symptoms*" is misleading because it implies that the product will improve or manage symptoms associated with anemia when this has not been demonstrated by adequate and well-controlled clinical studies.

OBP response summary: In the visual aid, this statement specifically refers to the anticancer therapies listed in the chart such as chemotherapy and bone marrow transplant. The statement does not refer to Procrit and the name Procrit or Epoetin alfa do not appear on this spread.

CBER/DDMAC response: Refer to item #1 above for the *Professional Print Advertisement* and *Visual Aid*

3. **CBER objection:** The claims that Procrit "*Makes all the Difference*" and "*Treatment Focuses on ... Maintaining Functional Abilities*" are misleading because they imply that the product will improve

or maintain health related quality-of-life when this has not been demonstrated by adequate and well-controlled clinical studies with validated instruments designed to measure quality-of-life parameters.

OBP response summary: "Makes all the Difference" refers to the treatment-related goal of "Meaningful Survival." Meaningful survival is a common goal of cancer therapy. The two-fold nature of "Meaningful Survival" is expressed by the following two sentences that appear on the professional print ad and the visual aid, "Newer chemotherapy treatment options have improved response rates and may extend survival. **Help provide *meaningful survival* during chemotherapy by treating anemia.**" Through the inclusion of these two sentences, it is clear that extending survival is attributed to chemotherapy. The benefit of Procrit is in managing anemia: a key toxicity of chemotherapy.

CBER response: Refer to item #1 above for the *Professional Print Advertisement* and *Visual Aid.* Note that, based on OBP's above response, the following statement includes the words "with PROCRIT" in the visual aid but not in the professional print ad, "Newer chemotherapy treatment options have improved response rates and may extend survival. **Help provide *meaningful survival* during chemotherapy by treating anemia with PROCRIT.**"

4. **CBER objection:** The bar graph depicting the increase in hemoglobin levels (page 6 in the visual aid) is misleading in the absence of contextual information regarding the percentage of patients who responded to therapy with 1.8 g/dl increases from baseline.

   OBP response summary: OBP agrees to include the above additional contextual information, if this presentation is made in the future.

   CBER response: OBP's response is acceptable.

Lack of Fair Balance

1. **CBER objection summary:** The DTC advertisements fail to disclose that Procrit is contraindicated in patients with uncontrolled hypertension. Furthermore, the DTC advertisements, professional print advertisements, and visual aid fail to disclose common side effects. Moreover, the printed materials are lacking fair balance because the risk information is not provided with a prominence and readability that is reasonably comparable to the presentations regarding the effectiveness and benefits of Procrit.

   OBP response summary: There are numerous examples of broadcast advertisements (Nexium, Imitrex and Celebrex) where contraindications or precautions are not mentioned in the advertisement or some but not all of the contraindications are mentioned. OBP believes that hypertension information is more relevant to the healthcare provider and therefore, OBP has included this disclosure in all of their professional pieces. Regarding the inclusion of additional side effect information, FDA has not issued guidance or regulations for determining what information should or should not be included when reporting side effects in a promotional context. OBP points to inconsistencies where the data reported varies considerably between products. Allegra and Zyrtex are given as examples. In light of these inconsistencies, OBP determined that the appropriate method for reporting such data is to look at side effects that were statistically different from placebo and to include such data in their promotional material. OBP would welcome the opportunity to provide comments in response to the publishing of draft guidance in the *Federal Register.*

   CBER response: OBP's response is not acceptable.

   DDMAC response: DDMAC is not swayed at all by OBP's response. OBP's argument is insulting. This is not a "cookie cutter" issue. The reference to needed guidance is ridiculous. This has to be done on a case-by-case basis.

   OCC/CBER response summary: OCC agrees with CBER's and DDMAC's response.

In accordance with 21 CFR 202.1 (e)(1), broadcast advertisements shall include information relating to the major side effects and contraindications of the advertised drug, therefore, OBP must include in their DTC broadcast advertisements the fact that Procrit is contraindicated in patients with uncontrolled hypertension. The side effects of diarrhea and edema mentioned in the current broadcast advertisements are acceptable as the major side effects since they are the only two that were statistically different between patients treated with Procrit and placebo-treated patients.

In accordance with 21 CFR202.1 (3)(iii), advertisements (we take this to include **print** advertisements) shall include information relating to side effects and contraindications and shall disclose each specific side effect and contraindication (which includes side effects, warnings, precautions, and contraindications. In this regard, common side effect such as fever, shortness of breath, paraesthesis and upper respiratory infection should be in included in the print advertisements in addition to diarrhea and edema and the contraindication for uncontrolled hypertension even though, as OBP mentioned, the Precautions section states that "*Hypertension, associated with a significant increase in hematocrit, has been noted rarely in cancer patients treated with Procrit. Nevertheless, blood pressure in patients treated wit Procrit should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease.*"

2. **CBER objection:** In the broadcast advertisements, the statements "Procrit is safe and effective" and "Procrit is proven and safe" immediately preceding the "major statement" minimize and undermine the communication of the subsequent risk information.

   OBP response: See response above under DTC Broadcast.

   CBER response: As long as the relevant safety information is there, "Proven and Safe" is OK. However, this response does not address the concern about minimizing and undermining the communication of subsequent risk information.

   DDMAC response: Discuss "framing" effects. Refer to item #3 under *DTC Broadcast Advertisements*.

   OCC **response summary:** OCC does not agree. OCC's response from item #3 under DTC Broadcast Advertisements is retyped here: OCC is not certain that CBER's objection is defensable. We may have a hard time arguing against proven and safe in context with risk information. We may not be on strong grounds to object to placement (in reference to framing effects), however, without proper context safe may be an issue and should be fixed with context.

3. **CBER objection:** The broadcast advertisement entitled, "Anthem" is lacking fair balance because the background audio interferes with and minimizes the risk information.

   OBP response: "Anthem" was discontinued in June 2001.

   CBER response: No action indicated.

"Adequate Provision" Requirement Not Fulfilled

1. **CBER objection:** For these widely disseminated DTC broadcast advertisements, "Coping" magazine is not considered to have a range of distribution wide enough to reach the targeted audience (i.e., including "newsstand" availability for consumers seeking anonymity). Therefore, dissemination of the DTC print advertisement component in this magazine does not fulfill the "adequate provision" requirement.

   OBP response summary: In the future, OBP will reference more general audience magazines given the fact that their print advertisements also appear in these types of magazines.

CBER response: OBP's response is acceptable.

2. **CBER objection:** The superimpositions of the print ad component and website component for partial fulfillment of the "adequate provision" requirement in the broadcast advertisements lack adequate prominence and readability.

   OBP response summary: OBP will endeavor to make the reference to the print compoent and the URL address even more prominent in future broadcast advertisements.

   CBER response: OBP's response is acceptable.

Failure to Adequately Disclose Prescription Drug Status

- **CBER objection:** In the DTC broadcast advertisements, the superimpositions regarding the prescription only status of the product lack adequate prominence and readability.
- **OBP response summary:** The claim, "by prescription" in the *Big Boy Bed* advertisement remained on the screen for 3.04 seconds as compared to an average of 3 seconds in other broadcast advertisements.
- **CBER response:** OBP's response is acceptable.

Consumer Friendly Language

- **CBER comment summary:** The statements, "*Procrit is for patients with non-myeloid cancers*" and "*It's for chemotherapy patients with non-myeloid cancers*" should be revised to be more understandable to the consumer (e.g., "forms of cancer that do not start in your bone marrow or certain types of cancers").
- **OBP response summary:** OBP is in complete agreement that DTC information be conveyed in consumer friendly language. In future broadcast advertisements, OBP will revise the claim to read, "Procrit...is for patients with most types of cancer."
- **CBER response:** OBP's response is acceptable.
- **DDMAC response:** The claim should be made in context. DDMAC suggests, for example in the current *Big Boy Bed* advertisement, to place the statement, "Procrit...is for patients with most types of cancer" immediately preceding the statement, "Ask your doctor about Procrit" or rather "Ask your doctor if Procrit is right for you."
- OCC response: OCC agrees that the statement suggested by OBP, "Procrit ... is for patients with most types of cancer" should immediately precede the statement suggested by DDMAC, "Ask your doctor if Procrit is right for you."

QUESTIONS FOR APLB:

The answers to OBP's questions are addressed in the above CBER, DDMAC and OCC responses.

1. **OBP question:** In order to understand FDA's perspective on the tagline "Strength for Living", it would be helpful if FDA would distinguish this tagline from similar claims in other currently running broadcast advertisements, e.g., "Your life is waiting" (Paxil) and "You can be stronger than diabetes (Avandia). What guidance can FDA provide to pharmaceutical companies regarding the outcomes study designs that were employed to support the above reference claims and similar claims that appear in many current broadcast and print advertisements.

   CBER response: Refer to item #1 under *General* above.

2. **OBP question:** What is FDA's standard for determining what a typical patient should look like for a disease category that is not clearly defined? Does FDA have a standard similar to the FTC's standard?

   CBER response: Refer to item #2 under *General* above.

   DDMAC response: DDMAC is not aware of a FTC standard.

3. **OBP question:** Does FDA believe that the model portrayed in a broadcast advertisement needs to comport with an image of someone currently receiving therapy for the disease or is it acceptable for a model to portray someone who has been successfully treated with a product, e.g., Lance Armstrong's advertisements for the BMS Oncology products?

   CBER response: Refer to item #2 under *General* above.

   DDMAC response: Not if typical of the disease state. Would take issue with the Lance Armstrong advertisements except this is a help seeking advertisement. Lance Armstrong is not typical. Also, Terrell Davis for a migraine drug is not typical of a migraine sufferer (Note: DDMAC did not allow this ad as Terrell Davis suffered a migraine, took the drug, then played in the Super Bowl. This would not be possible, so was considered extremely misleading).

4. **OBP question:** Is there a regulation that prohibits the discussion of symptoms associated with a disease in a branded advertisement? If there is no regulation on point, what guidance does FDA have regarding the linkage between the discussion of symptoms and a statement of the approved indication?

   DDMAC response: There is no specific guidance. If saying yes, they did not measure strength, why can't they say symptoms? Per Laurie Burke, do not allow symptom claims unless they are measured. Have to have outcome data with symptom as an endpoint.

5. **OBP question:** What data did FDA rely upon in order to determine that the claim "natural" would be interpreted by consumers to mean that Procrit is safer or more effective than other products to increase red blood cells? Did FDA evaluate the use of "natural" in other pharmaceutical advertisements and, if so, did the agency reach a similar conclusion?

   CBER response: Refer to item #1 under *DTC Broadcast Advertisements* above.

6. **OBP question:** We request that FDA share the objective data it relied upon to conclude that consumers, particularly cancer patients, "lack the background" to understand the intended meaning of proven and safe. What did FDA rely upon in distinguishing the use of the claim of "proven" in the referenced Procrit advertisement from its use in other currently running broadcast and print advertisements?

   CBER response: Refer to item #3 under *DTC Broadcast Advertisements* above.

7. **OBP question:** Does FDA have specific objections to claims regarding proven efficacy outcomes associated with cancer chemotherapy agents? If no, may data that supports the survival rates with chemotherapy agents are presented in promotional materials that discuss, not only the agents, but also includes a discussion of chemotherapy toxicities?

   CBER response: Refer to item #1 under *Professional Print Advertisement* and *Visual Aid* above.

8. **OBP question:** What is FDA standard for determining the appropriate fair balance presentation for print and broadcast advertisements? Will FDA be publishing this standard as draft guidance in the Federal Register in the near future?

   CBER response: Refer to item #1 under **Lack of Fair Balance** above.

DDMAC *response*: No, FDA will not be publishing draft guidance.

Firm name: Amgen – Ortho Biotech Products, L.P.

Letter type: Review Memorandum

bcc: HFM-602
DCC (HFM-99)

History:
Prepared by: C Broadnax 3/19/02, 3/20/02, 3/21/02, 3/22/02, 3/25/02,3/28/02, 4/1/02, 4/3/02
Comments by: M. Malarkey 3/27/02
Comments by: T. Stifano 4/1/02
Finalized by: C. Broadnax

File name: (P10201011, P10201025, P10827003, P10828003, P11001014, P11220001, P11220002, P111220003)

Address: \\Cbs5055682\OC\APLB\APLB\BROADNAX\PROCRIT\Procrit 21DEC01 Advisory Letter REVMEM.DOC

Concurrence box:

MailCode or Office	Name	Date

MailCode or Office	Name	Date

Broadnax, Carole

rom: Broadnax, Carole
Sent: Tuesday, May 28, 2002 2:58 PM
To: Byrd, Glenn *; Abrams, Thomas W
Cc: Stifano, Toni; Malarkey, Mary
Subject: RE: Ortho - Procrit

Tom,

In preparation for tomorrow morning's teleconference call with DDMAC, I am forwarding to you the attached review memorandum regarding CBER, DDMAC's and OCC's assessment of the Amgen/Ortho January 2002 response letter to CBER's December 21, 2001 advisory letter. This review memorandum was the basis for CBER's teleconference call with Amgen/Ortho on April 11, 2002.

It is my understanding that tomorrow's teleconference with DDMAC will focus on OCC's viewpoint of the issues.

Carole

Procrit
EC01 Advisory Le

-----Original Message-----
From: Byrd, Glenn *
Sent: Tuesday, May 28, 2002 12:10 PM
To: Abrams, Thomas W
Cc: Stifano, Toni; Malarkey, Mary; Broadnax, Carole
Subject: Ortho - Procrit

Tom,

HI. I understand there was a discussion planned for today on this topic; however, Carole had to attend a follow-up meeting to an Advisory Committee from last week, thus she is out of the office today and unable to participate. Her role is key to any discussions so can we please re-schedule?

Please reschedule any discussion involving Procrit and Ortho promotional matters through me.

Thanks,

Glenn Byrd
Chief, Advertising and Promotional Labeling Branch
Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Woodmont Office Complex 1
1401 Rockville Pike, HFM-602, Rm. 235S
Rockville, MD 20852-1448
301-827-6059
byrdg@cber.fda.gov

TC w/ DDMAC. 5/29/02
re: Procrit

TC requested by DDMAC. ~~[illegible]~~ want to know outcome re: OCC's opinion

DDMAC may flu w/ CBER p̄ TC.

~~[illegible]~~: ~~Big~~ Overall message fr. OCC - ~~[illegible]~~ to find middle ground - fix in context rather than yanking material

Mary Malarkey

DDMAC?: who in OCC does CBER deal w/ Seth Ray & M. Raza

DDMAC's timeframe 28 to 60 calender days for 4 NOV ltrs.
3/4 ltrs needed flu & more info w/ OCC.
Seth Ray & Mike Landa review DDMAC's draft ltr.

5th NOV has past timeframe of 45 working days (Came back w/ comment fr. OCC at 40 days)
Unapproved drug ~~not~~ unapproved use.

P20731013

Ralph Snalling
Vice President
Regulatory Medical Affairs

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.1000
Direct Dial [ ]
Fax [ ]

May 10, 2002

MAY 14 2002
85982

Mary A. Malarkey, Director
Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

RE: Follow-up to April 11, 2002 teleconference

Dear Ms. Malarkey:

Ortho markets Procrit® (Epoetin alfa) through a product license agreement with Amgen. Ortho has asked Amgen to transmit the following for your consideration:

Reference is made to the April 11, 2002 teleconference, between FDA/CBER (FDA) representatives and employees of Amgen Inc., J&J Pharmaceutical Research & Development L.L.C. (J&JPRD) and Ortho Biotech Products, L.P. (OBP), regarding PROCRIT® (Epoetin alfa) promotional materials. The purpose of the teleconference was to facilitate discussion on and closure of the issues you raised in your change of opinion letter of December 21, 2001 and OBP's response letter of January 22, 2002.

The participants from FDA/CBER were Carol Broadnax, Mark Raza, Esq., Toni Stifano and Mary Malarkey. The participants representing OBP/J&JPRD and J&J Corp. were Minnie Baylor-Henry, Liz Barrett, Matthew Quilty, Shelley Reagan, Brenda Sarokhan, and Kathy Schroeher, Esq. The representatives from Amgen were Becky Cleavenger, Robert Church, J.D. and John Weidenbruch, J.D.

The following represents OBP's summary of the issues discussed and decisions reached during the teleconference:

General

- Regarding the "Strength for Living" tagline, FDA agreed that there is no suggestion of survival. However, since FDA equates "strength" with energy, it was proposed that the claim would be placed in closer proximity to the Procrit indication, so it is clear that the reference is to the symptoms of the anemia associated with our approved indication. FDA agreed and requested that OBP send samples of the tagline positioning. In accordance with the request, OBP has enclosed a broadcast ad storyboard and DTC print ad for FDA's review and comment *(See Attachments 1 and 2)*.
- FDA clarified that they have no issues with the patient model used in the *Big Boy Bed* ad, but believe that all of the models depicted in *Anthem* were not considered representative of chemotherapy patients. FDA stated that in an ad with multiple models, the surrounding text is important and the appropriateness of the models in such an ad will be considered on a case-by-case basis. When the models have a full head of hair, for example, this may misrepresent the patient population. While you indicated that the patient models do not have to be bald, it was clear that FDA would be more amenable to a favorable consideration, if the patient models depicted previous cancer patients versus those that depict current chemotherapy patients. OBP confirmed that the *Anthem* ad was discontinued and there are no current plans to use it in the future. However, if OBP decides to use an ad with multiple models, FDA's guidance will be taken into consideration.

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- Regarding claims or implications that Procrit treats weakness and fatigue, FDA does not object to discussion of symptoms of anemia, as agreed during our previous teleconference on October 19, 2000. However, FDA reiterated the importance of linking the indication to the first mention of symptoms. OBP stated that since the previous discussion of this issue over a year ago, it had been very consistent in linking symptoms to the disease and treatment in the same textual area. However, in the future, we will link the information even closer to the indication *(See Attachments 1 and 2)*.

- Use of "natural" is acceptable to FDA, but it should not modify Procrit. OBP agreed to submit proposed language. Accordingly, the following example is provided for FDA to review and comment *(See Attachments 1 and 2)*:

  "Procrit helps you build red blood cells the same way your body does naturally"

Professional Print Advertisement

Visual Aid

- FDA has no objection to the clinical information presented in the professional visual aid. However, the disease state information needs to be separated from the Procrit information. You indicated that the Procrit logo and the bolded statement "Helps provide meaningful survival during chemotherapy by treating anemia with PROCRIT" needs to be removed from the front cover. However, you agreed that the Procrit logo could remain on the back cover. It was noted that similar revisions would be needed in order to address the same issue in the 2-page professional journal ad. Attached, is a revised draft layout of the visual aid and professional print ad for your review and comment (*See Attachments 3 and 4*).

- As stated in the response letter, the bar graph (page 6 of the visual aid) will be revised to include the contextual information, if this presentation is made in the future *(See Attachment 3)*.

- *Lack of Fair Balance* – As stated in the OBP January response letter, the *Precautions* section of the PI states that hypertension is rarely reported in cancer chemotherapy patients, nevertheless, patient blood pressure, particularly those with an underlying history of hypertension or cardiovascular disease, needs to be carefully monitored.

  The contraindication is clearly referencing the Nephrology patients. This position is supported by language in the Summary Basis for Approval (SBA) for CRF; the first Epoetin alfa approved indication *(See Attachment 6)*. In the nephrology studies, hypertension was the most frequently reported adverse event in the Epoetin alfa treated patients and placebo patients. In response to our clear recognition of the intended PI language, we have referenced hypertension in the nephrology professional and DTC fair balance statements.

  In contrast, the SBA for the Cancer Chemotherapy indication shows that hypertension was rarely reported in this patient population. Please note that hypertension is not included in the adverse event chart *(See Attachment 5, pages 4 and 5 respectively)*.

  In addition, we continue to believe that we have appropriately disclosed the significant adverse events. Diarrhea and edema were the only two events that were statistically different than placebo.

- FDA does not object to the claims of "safe and effective", *per se*, or variations thereof, but recommends that these claims be closely aligned with the risk information associated with the product. OBP agrees to do so.

- The following changes will be made to the adequate provision in future broadcast ads:
  - *Saturday Evening Post* will replace *Coping* as the magazine reference for the print ad.
  - The prominence of the reference of the print and URL component will be increased.
  - The prescription only status will continue to be prominently disclosed.

OBP agrees with FDA that DTC information needs to be conveyed in consumer-friendly language. Therefore, in future broadcast advertisements, OBP will revise the referenced claim to read, "Procrit is for patients with most types of cancer."

As previously stated in our January response letter, OBP agrees to include the dosage form, ie, injectable, at the first display of the brand and generic name in future broadcast advertisements.

In closing, OBP and FDA agreed that the implementation of this agreement will begin when resolution is reached on all of the remaining issues. When agreement is reached, OBP will revise all referenced pieces consistent with such agreements, within 90 days or at the next printing, whichever comes first.

Should you have any questions or require further information, please contact either Becky Cleavenger or myself at (805) 447-2442 or 447-3058, respectively, or by FAX at (805) 498-9377.

Sincerely,

for/ Ralph Smalling
Vice President,
Regulatory Affairs

2002-0510_BC_GC_OrthoTeleconFU

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

July 30, 2002

Mr. Ralph Smalling
Vice President, Regulatory and Medical Affairs
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Smalling:

This letter is in regard to your May 10, 2002, letter sent in response to the April 11, 2002, teleconference between representatives from the Center for Biologics Evaluation and Research, FDA, and representatives from Amgen Inc., J& J Pharmaceutical Research and Development L.L.C. and Ortho Biotech Products, L.P. (OBP) concerning the promotion of Procrit (Epoetin alfa). The April 11, 2002, teleconference was initiated to discuss the issues raised in OBP's letter received January 25, 2002, in response to the Division of Case Management's (DCM) letter of December 21, 2001. We have reviewed your May 10, 2002, response and find that the majority of your corrective actions are acceptable, however, we have comments on the following remaining issues:

General

The tagline "*Strength for Living*" should be presented in close proximity to the indication statement (which would place the intent of the phrase in the proper context) as discussed during our April 11th teleconference. As presented, it remains unclear that the "strength" one gains is in reference to the symptoms of anemia associated with the treatment of anemia in cancer patients on chemotherapy [the approved indication]. The tagline in the revised "Big Boy Bed" direct-to-consumer (DTC) television (TV) broadcast advertisement (ad) and the DTC print ad remains in the same position as was cited in DCM's December 21, 2001 letter. We again request that the tagline be repositioned to be closer to the indication as agreed during the April 11th teleconference.

Revised Draft Visual Aid ("Hematologic Malignancies")

In order to ensure that the discussion about the disease state is separated from the Procrit information:

1. Please move the indication statement from the front cover of the visual aid to the first mention of Procrit on page 6.

2. Please revise page 3 as indicated:

a. Please move the table "Incidence of Anemia with NHL Chemotherapy Regimens Is High" above the information for "Anemia Impacts Outcomes" and "Manage Anemia – To Balance Treatment Goals With *Meaningful Survival* During Chemotherapy" as a transition from the discussion of chemotherapy regimens on page 2 to the discussion of anemia on page 3.

b. Please revise the second bullet point under "Anemia Impacts Outcomes" to read: "*It is one of several clinically important* prognostic factors for survival in lymphoma" to clarify that there are other clinically important prognostic factors for survival in lymphoma in addition to anemia.

c. Please delete "With *Meaningful Survival*" from the second subheader to read: "Manage Anemia – to Balance Treatment Goals During Chemotherapy." Otherwise, the statement may still misleadingly imply that management of anemia with Procrit will provide meaningful survival.

d. Please delete "Is High" from the table title to read: "Incidence of Anemia with NHL Chemotherapy Regimens"

e. Please revise the second bullet point under "Manage Anemia – To Balance Treatment Goals With *Meaningful Survival* During Chemotherapy" to read: "With repeated exposure to non-platinum-based chemotherapy, this approaches 66% *(see Table)*"

f. In addition, page 5 should also be revised accordingly.

3. Please revise the third bullet point on the back cover of the visual aid to read: "*Chemotherapy* treatment often requires long term therapy, and focuses on prolonging survival." Otherwise this statement misleadingly implies that the "treatment" is Procrit.

4. Please revise the fourth bullet point on the back cover of the visual aid to read: " AIM with PROCRIT – to optimize hemoglobin response and help *treat anemia* during chemotherapy." Otherwise, this statement misleadingly implies that aiming with Procrit helps to provide meaningful survival during chemotherapy.

5. Please include on the back cover a revised indication statement from the front cover "Procrit – For chemotherapy induced anemia in patients with nonmyeloid malignancies." Otherwise, in the context of the "Meaningful Survival" claim and the Procrit logo, the back cover still misleadingly implies that Procrit will provide meaningful survival by treating anemia.

6. We ask that you submit another revised visual aid for review before going to final print.

Revised Draft Professional Print Advertisement

Please delete the "MEANINGFUL SURVIVAL" claim or revise the "MEANINGFUL SURVIVAL" and "Makes *all* the Difference" claims to read: "Makes a Meaningful Difference" or similar wording. Otherwise, the ad still misleadingly implies that treatment with Procrit provides "MEANINGFUL SURVIVAL". It is not possible to dissociate the Procrit logo on the adjacent page from the "Meaningful Survival" claim on the first page. The statement under the "Makes all the Difference" claim that reads: "Because newer chemotherapy treatment options have improved response rates and may extend survival, providing survival that is *meaningful* has become an important treatment goal" is of too small a type size to provide an adequate association between newer chemotherapy treatment options and the larger type size "MEANINGFUL SURVIVAL" claim.

Lack of Fair Balance

1. For the DTC print ads and professional promotional labeling and print ads, the regulations specify that information about risks must include each specific side effect and contraindication for the product's approved labeling. The regulations also clarify that the terms "side effects and contraindications" when used in that section include information contained under the sections addressing side effects, warnings, precautions, and contraindications; therefore, please add language from the Precautions section of the package insert that, "Hypertension, associated with a significant increase in hematocrit, has been noted rarely in cancer patients treated with Procrit. Nevertheless, blood pressure in patients treated with Procrit should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease." This information is more accurate for the cancer patient.

   Please add the following adverse experiences in addition to the adverse experiences of diarrhea and edema even though these were statistically significantly different between Procrit treated patients and placebo treated patients:

   pyrexia (possible DTC wording: fever), vomiting, shortness of breath, paresthesia (possible DTC wording: an abnormal sensation such as burning, pricking, tickling, or tingling) and upper respiratory infection.

   These adverse experiences occurred more frequently with Procrit treated patients compared to placebo treated patients.

2. For the TV DTC broadcast ad, the side effects of diarrhea and edema are acceptable as the major side effect information since they are the only two that were statistically different between patients treated with Procrit and placebo-treated patients.

3. Please be reminded that any statement of risk information needs to be in close proximity to any claims of "proven and safe" or "safe and effective" or any variations of these claims.

We acknowledge that when final agreement is reached on these remaining issues that OBP will revise all Procrit promotional materials that contain the same or similar claims or presentations within 90 days or at the next printing or taping, whichever comes first.

Within 10 days of the date of this letter, please notify APLB in writing with your intent to comply with this request.

Your written response should be sent to the attention of Mr. Glenn Byrd, Chief, APLB, at the following address.

Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
Advertising and Promotional Labeling Branch, HFM-602
1401 Rockville Pike
Rockville, MD 20852-1448

We remind you that only written communications are considered official.

Sincerely,

Mary A. Malarkey
Director
Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Minnie Baylor-Henry, R.Ph., J.D.
Sr. Director, Regulatory Affairs
Advertising and Promotion Review
The R.W. Johnson Pharmaceutical Research Institute
Route 202, P.O. Box 300
Raritan, NJ 08869-0602

Ralph Smalling – Page 5

Firm name: Amgen Inc.

Letter type: Untitled

bcc: HFM-602 [redacted]
HFM-602
HFM-602
HFM-99
HFM-48
HFM-610
HFM-610
HFM-573

C. Broadnax
G. Byrd
APLB Letter File
APLB Complaint File
DCC
OCTMA
DCM Clipboard
M. Malarkey
S. Litwin

History:
Prepared by: C. Broadnax: 5/30/02, 6/3/02, 7/22/02, 7/24/02, 7/29/02
Comments by: G. Byrd: 6/3/02, 7/23/02
Comments by: T. Stifano: 6/11/02, 7/26/02
Comments by: M. Malarkey: 7/29/02
Finalized by: C. Broadnax: 7/29/02

File name: (P10201011, P10201025, P10827003, P10828003, P11001014, P11220001, P11220002, P111220003)
Address: Cbs\5055682\OC\APLB\APLB\broadnax\Procrit\Procrit Anthem Ortho Follow-up Response Letter – final.doc

Concurrence box:

MailCode or Office	Name	Date
HFM-602	Broadnax	7/29/02
610	Malarkey	7/30/02

MailCode or Office	Name	Date

Senger, Jeffrey

From: Troy, Daniel E. [DTroy@Sidley.com]
Sent: Tuesday, February 27, 2007 11:33 AM
To: Senger, Jeffrey
Subject: FYI re the promotional issue we discussed

A woman named Leah Walker from Amgen has asked for a meeting with Tom Abrams, Lesley Frank, and Mark Askine from DDMAC. They have asked for someone from OCC to be involved. It would be great if you could make sure that someone at OCC makes sure that people understand the limits of their authority. I will keep you posted about what I hear.

Thanks so very much

Dan

Sent from my BlackBerry Wireless Handheld

Sidley Austin LLP mail server made the following annotations on 02/27/07, 10:30:22:

IRS Circular 230 Disclosure: To comply with certain U.S. Treasury regulations, we in
that, unless expressly stated otherwise, any U.S. federal tax advice contained in th
communication, including attachments, was not intended or written to be used, and ca
used, by any taxpayer for the purpose of avoiding any penalties that may be imposed
taxpayer by the Internal Revenue Service. In addition, if any such tax advice is us
to by other parties in promoting, marketing or recommending any partnership or other
investment plan or arrangement, then (i) the advice should be construed as written i
with the promotion or marketing by others of the transaction(s) or matter(s) address
communication and (ii) the taxpayer should seek advice based on the taxpayer's parti
circumstances from an independent tax advisor.

****
This e-mail is sent by a law firm and may contain information that is privileged or
If you are not the intended recipient, please delete the e-mail and any attachments
immediately.

****

Beckerman, Peter

From: Senger, Jeffrey
Sent: Monday, February 26, 2007 6:41 PM
To: Beckerman, Peter
Cc: Bradshaw, Sheldon
Subject: RE: Dan Troy

Pete,
Dan just called me, and he was not on the CDER call. He also says that CDER wants a warning on both on-label and off-label indications, even though there is no scientific data supporting a problem with on-label use in renal treatment. He claims this goes against what Bob Temple and Rachel Behrman have been saying regarding the physician labeling rule. Do you know anything about this?
Thanks,
Jeff

-----Original Message-----
From: Beckerman, Peter
Sent: Monday, February 26, 2007 2:40 PM
To: Senger, Jeffrey
Cc: Bradshaw, Sheldon
Subject: RE: Dan Troy

Sure -- Do either of you know if Dan was on the call?

-Pete

-----Original Message-----
From: Senger, Jeffrey
Sent: Monday, February 26, 2007 12:53 PM
To: Beckerman, Peter
Cc: Bradshaw, Sheldon
Subject: RE: Dan Troy

Pete -- here is Sheldon's response. Can someone make a clarifying call?
Thanks,
Jeff
cc: Sheldon

-----Original Message-----
From: Bradshaw, Sheldon
Sent: Monday, February 26, 2007 12:49 PM
To: Senger, Jeffrey
Subject: RE: Dan Troy

I don't think a writing is necessary, but if someone on the call thought they heard an order, I don't think it would hurt to simply place a call to that individual clarifying that it was a request.

-----Original Message-----
From: Senger, Jeffrey
Sent: Monday, February 26, 2007 12:34 PM
To: Bradshaw, Sheldon
Subject: FW: Dan Troy

Here's Pete's response. He talked with Mark Askine of DDMAC, who was also on the call, who said Pazdur did not phrase it as an order. Let me know if/how you would like me to follow up.
Jeff

-----Original Message-----
From: Beckerman, Peter

Sent: Monday, February 26, 2007 11:31 AM
To: Senger, Jeffrey
Subject: RE: Dan Troy

I believe it was oral -- and for what its worth, Mark Askine did not report hearing this as an order. Dan well knows what the limits of FDA's authority are, and for what its worth, I don't think much is to be gained by requiring a writing that highlights those limits.

-----Original Message-----
From: Senger, Jeffrey
Sent: Monday, February 26, 2007 11:30 AM
To: Beckerman, Peter
Subject: Fw: Dan Troy

Here's Sheldon's followup -- thoughts?

----- Original Message -----
From: Bradshaw, Sheldon
To: Senger, Jeffrey
Sent: Mon Feb 26 11:08:16 2007
Subject: RE: Dan Troy

Was Rick's original statement in writing or did he make it orally? Given the confusion, he should probably issue a clarification.

From: Senger, Jeffrey
Sent: Monday, February 26, 2007 11:02 AM
To: Bradshaw, Sheldon
Subject: FW: Dan Troy

Here's Pete's response:

From: Beckerman, Peter
Sent: Monday, February 26, 2007 10:57 AM
To: Senger, Jeffrey
Subject: RE: Dan Troy

I don't, Jeff. -- I haven't spoken to Rick, having gotten my information from Mark Askine, the DDMAC representative who was on the call. As I mentioned, I spoke to Michael Petty, from Amgen, and he was satisfied with that -- he didn't request any clarification from Pazdur, so I doubt that there is any intent to issue any such clarification.

-Pete

From: Senger, Jeffrey
Sent: Monday, February 26, 2007 9:46 AM
To: Beckerman, Peter
Subject: FW: Dan Troy

Hi, Pete. Do you have any info on Sheldon's question?
Thanks,
Jeff

From: Bradshaw, Sheldon
Sent: Monday, February 26, 2007 9:31 AM
To: Senger, Jeffrey
Subject: RE: Dan Troy

Was Rick going to clarify that this was only a request, not an order?

From: Senger, Jeffrey

Sent: Friday, February 23, 2007 6:42 PM
To: Bradshaw, Sheldon
Subject: Dan Troy

Hi, Sheldon. Just after I talked with you, Pete Beckerman came into my office and gave me the whole story on this. The person who made the call was Rick Pazdur, the head of the Office of Oncology Drug Products, but Dan and others may have misunderstood what he said (or at least what he meant to say, which was that this was only a request, not an order). The dispute is over the wording of a new black box warning following some safety studies, and it sounds like CDER is working on it expeditiously. I called Dan and left a message, but he hasn't called back yet. I can tell you more next week if you like.
Jeff

Ray, Seth

From: Ray, Seth
Sent: Wednesday, June 20, 2007 10:04 AM
To: Bradshaw, Sheldon; Raza, Mark
Cc: Ray, Seth
Subject: Draft EPO Q & A [Sheldon Please Read]

Sheldon - OK 6/20

Attachments: EPOWaysand MeansQandA.doc

I would make two changes to the first Q & A: (1) For clarity, at the end of the question, I would insert "in cancer patients"? (2) In the answer, I would delete clause (2) ("the fact that there was certain information concerning weakness/fatigue already in the product's labeling"). As Mark and I discovered yesterday, the quality of life (QOL) information in the Clinical Experience section of the Procrit PI only applies to the renal failure indication. [In fact, CBER turned down Amgens's supplements to add QOL claims regarding the cancer/chemotherapy indication.] In addition, a Q & A prepared by CBER makes a strong case that, because of marked differences in the nature of the renal failure and cancer/chemotherapy anemia indications, it is not reasonable to infer improved QOL from one indication to another. [FYI--There was broad QOL information in the patient labeling for Procrit, but it was not added until 5 years after the CBER letter was sent.]

Seth

From: Raza, Mark
Sent: Tuesday, June 19, 2007 5:02 PM
To: Ray, Seth
Subject: RE: Please remind me when CBER products (EPO) were transferred to CDER. Thanks

Sheldon gave me some general comments verbally. I tried to incorporate them. I stop by to briefly discuss with you.

EPOWaysand
eansQandA.doc (32

From: Ray, Seth
Sent: Tuesday, June 19, 2007 3:46 PM
To: Raza, Mark
Subject: RE: Please remind me when CBER products (EPO) were transferred to CDER. Thanks

Great, thanks.

From: Raza, Mark
Sent: Tuesday, June 19, 2007 2:18 PM
To: Ray, Seth
Subject: RE: Please remind me when CBER products (EPO) were transferred to CDER. Thanks
Importance: High

Seth - Sheldon gave me verbal comments on my draft Qs and As. I will revise and provide to you.

From: Ray, Seth
Sent: Tuesday, June 19, 2007 11:34 AM
To: Raza, Mark
Subject: RE: Please remind me when CBER products (EPO) were transferred to CDER. Thanks

thanks

From: Raza, Mark
Sent: Tuesday, June 19, 2007 11:32 AM
To: Ray, Seth

Comprehension of Prescription Drug Information: Overview of A Research Program

Ruth S. Day

Duke University
Box 90085, Durham, NC 27708-0085
ruthday@duke.edu

Abstract

Both patients and healthcare professionals must understand information about prescription drugs to help them use medications in a safe and effective manner. However drug information materials can be difficult to understand – they can be long, detailed, technical, and complex. Comprehension problems can increase the chances that ineffective treatment or medication errors will occur. This paper presents an overview of a large-scale research program on how people understand drug information, especially benefits and risks. It describes basic cognitive principles used to evaluate drug information and shows ways to make it easier to understand and use. Two key concepts underlie this work, ***cognitive accessibility*** and ***alternative representations***. They are described and illustrated with sample experiments on comprehension of pharmacy leaflets, TV ads, medication schedules, and side effects.

Basic Problem

Both patients and healthcare professionals must understand information about prescription drugs to help them use medications in a safe and effective manner. However information for a given drug can be difficult to understand – it can be long, detailed, technical, and complex. For example, the "professional labeling" for a prescription drug, the key document in approval by the Food and Drug Administration (FDA), has multiple pages of detailed information such as indications and usage, dosage and administration, warnings, precautions, contraindications, adverse reactions, use in special populations, clinical pharmacology, and drug interactions.

Drug information documents designed for patients such as pharmacy leaflets (also known as consumer medical information, or CMI) are generally shorter, less detailed, and less technical. Nevertheless they are often difficult to understand, remember, and use as well.

Inadequate comprehension by both professionals and patients can increase the chances that ineffective treatment or medication errors will occur. Especially important is information about the potential benefits and risks of drugs. For example, a physician must determine whether the benefits of a drug outweigh its risks for a specific patient in order to make an appropriate prescribing decision. Patients must know something about possible side effects, so they can make an informed decision about treatment, monitor for possible side effects, and take appropriate action if any occur (such as seeking immediate medical attention vs. just waiting for them to resolve).

To what extent do people understand both the benefits and risks of prescription drugs? Our research shows that they understand benefits much better than risks. Various factors may contribute to this discrepancy, such as the nature of risk information itself (its complex and technical nature) or possible emotional reactions (fear of negative health outcomes). However this research examines the "cognitive accessibility" of drug information – the ease with which people can find, understand, remember, and use it [1]. The ultimate goal is to use the information in an accurate, safe, and effective manner. Without good comprehension of the information this goal can be difficult at best.

Of particular interest is how information about drug benefits vs. risks is provided. Are they in "fair balance?" That is, are they provided in equally accessible ways? Therefore we examine various aspects of existing drug information materials (Original Displays) that can facilitate or inhibit cognitive accessibility. When we find problems, we redesign part or all of the materials to increase cognitive accessibility (Enhanced Displays). Then we test comprehension of both displays in laboratory experiments. We use the "alternative representations" approach [2] in this work, retaining the same information in both displays but providing it in different ways, as described more fully below.

Some basic cognitive principles underlie this research. They are described briefly below and are illustrated by an experiment on comprehension of pharmacy leaflets. The key concepts of *cognitive accessibility and alternative representations* are also described, with sample experiments on comprehension of TV ads, medication schedules, and side effects. Although the research program

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studies both professionals and patients and over-the-counter (OTC) drugs as well as prescription (Rx) drugs, the focus of this paper is on patient comprehension of Rx drugs.

Research Approach

Sources of Drug Information

We examine a wide variety of information sources for drugs. Consumer-oriented materials include pharmacy leaflets, patient package inserts, Medication Guides (required for drugs with serious risks) and direct-to-consumer (DTC) advertising including TV ads, magazine ads, and product websites. Other materials are intended for healthcare professionals such as the professional labeling (often reprinted in the *Physicians Desk Reference*), compendium manuals such as *Drug Facts and Comparisons* and *USP Drug Information*, and various drug safety alerts such as the *Dear Healthcare Professional* letter. We examine the same types of information across all these sources, especially benefits vs. risks.

Research Phases

Cognitive Analysis Phase. First we analyze existing information (Original Display) for a given drug in terms of basic cognitive principles such as information load, chunking, coding, location, and form of representation, as described below. For example, we generate quantitative measures for various cognitive factors in a pharmacy leaflet, then calculate the cognitive accessibility of the entire document as well as for specific content such as benefits and risks.

Enhanced Display Phase. Next we redesign the information to enhance its cognitive accessibility as needed, based on cognitive principles (Enhanced Display). For example we might display a given section in an alternative format, reorder some information, or introduce contrasting fonts to demarcate various sections. However we do not change the information itself – we just make it more cognitively accessible.

Cognitive Experiment Phase. Finally we perform experiments to test the effects of the Original Display vs. the Enhanced Display on various cognitive processes including attention, comprehension, memory, problem solving, and decision making. Typically we use a Study-Test paradigm, where people study a document or video, then participate in standard or novel experiment paradigms such as search-and-find, free report, and scenario tasks. Sometimes we use multiple tasks to assess types of knowledge for important content domains, such as risks.

Research Participants

Participants vary widely in age (18-80), education (6th grade education through postdoctoral training), health status (healthy nonpatients vs. patients with a specific health condition), knowledge about medical and pharmaceutical information (laypersons vs. professionals), economic levels, and work experience. For example, some are literate young adults with only a layperson's knowledge about health treatments and no serious health conditions while others are community-dwelling adults who are currently taking a specific drug to treat a diagnosed health condition. Patients with specific health conditions should be especially motivated to understand the benefits and risks of the drug they are currently taking. However we find that the same general patterns of results occur when testing patients on their own drug vs. an unrelated one and for patients vs. nonpatients.

Professionals in this research include physicians, pharmacists, and others who possess considerable knowledge about prescription drugs. As expected they perform better overall, yet still show the same general patterns – better on some types of information than others, with similar types of errors. Despite their knowledge and expertise, they are still affected by the same cognitive accessibility factors.

Basic Cognitive Principles

To examine the cognitive accessibility of any drug information source, we begin by observing the extent to which it uses well-known cognitive principles in an effective manner. For example, people generally have more difficulty processing passive sentences than active ones [3], so we count the percentage of sentences in passive vs. active voice; a high score indicates lower cognitive accessibility. Although there are sometimes disagreements about why a given phenomenon occurs, the findings are robust and have stood the test of time – in some cases for over a half century. Below are just a few of the basic cognitive phenomena and principles used in this research. They are described here briefly, with more details and background information provided elsewhere [4].

Experimental vs. Naturalistic Materials

Many basic cognitive phenomena and principles are very robust – they are highly replicable, have stood the test of time (sometimes for over a half century), and occur across many experiment conditions. Investigators typically use highly restricted test materials to examine these classic phenomena such as numbers, words, objects, or simple sentences. Some use more complex materials such as

descriptive paragraphs or narratives, but they are still generated in the lab and are tightly controlled to test specific factors or theoretical constructs.

In contrast, the drug information research reported here begins with very complex materials that are already being used in the real world (Original Displays). It evaluates their accessibility using cognitive principles and tests them as-is in the laboratory, even though they are not as tightly controlled as standard laboratory materials. Subsequent experiments isolate specific sections or features of the Original Displays and vary them systematically with Enhanced Displays to test cognitive principles.

Information Load and Cognitive Load

Too much information can overload people so that they do not "get" much of it or even stop trying to do so. This is especially so if it is technical in nature, such as information about prescription drugs. How much is "too much" information? It is tempting to try to answer this question in terms of *information load*, such as the number of words or pages in a print or spoken communication. However it is not information load *per se* that is important, but instead *cognitive load*.

Cognitive load as used here refers to mental effort, such as the number of mental operations required for a task and their difficulty (for applications to instructional design see [5]). A heavy cognitive load can make information harder to understand, remember, and use. We can lighten cognitive load by using cognitive principles to enhance the accessibility of the information. Thus a longer document (heavy information load) with high cognitive accessibility indicators can be easier to process that a shorter one with low cognitive accessibility.

Clusters, Categories, and Organization

Clustering involves keeping like-information together. When people see word lists with items from several semantic categories (such as vegetables, professions, furniture) but in random order, they tend to recall items from the same category together even though they occurred randomly throughout the list [6]. In general, people do better with information already organized into semantic categories; for a review of some classic findings, see [7].

Chunking

Chunking involves separating a packet of information from nearby information, either in space (visual information) or time (auditory) [8]. Chunking of information can improve memory and other cognitive functions. For example, a list of digits such as 854326197 will be harder to remember than the same digits chunked as 854-326-197.

Coding

Once a given packet of information has been formed and chunked, it is often helpful to give it a brief descriptive name. Naming helps people encode the information, understand it, store it, and retrieve it later. Linguistic codes can be especially useful if used in an effective manner. For example, "side effects" is a good name for unwanted events such as dizziness and nausea, rather than "problems" which could refer to problems with side effects, dosing, existing health conditions, or the concomitant use of other drugs.

An appropriate code can depend on the knowledge and experience of the user. For example, a section might be called "side effects" in a patient leaflet and "adverse events" in a professional document. A bad code – or none at all – can mean that users miss the information when viewing it and/or lose it shortly thereafter.

Location (Order Effects)

When given a list of items, people generally recall the items at the beginning and ends of the list best and have trouble with ones in the middle. This classic "serial position effect" is a very robust phenomenon and has been replicated many times (for example, see [9]). Although information in the middle of a series is usually not retained well, this effect can be ameliorated or reversed by enhancing it in some way, such as presenting it in a different color [10].

Linguistic Complexity

Many options for linguistic expression have cognitive consequences. In general, sentences that are more grammatically complex, have more propositions (idea units), and more unfamiliar words are harder to understand and remember. We analyze various linguistic parameters of written and spoken language about prescription drugs. Some of these measures are difficult and time-consuming to obtain such as propositional analyses [11], so we also include very simple measures that are easy to obtain, correlate with more sophisticated measures, and can serve as a quick proxy for comprehensibility [12].

Experiment 1 – Basic Cognitive Processes: Pharmacy Leaflets

Some of our research on pharmacy leaflets [13] illustrates the effects of several basic cognitive principles on comprehension and memory for drug information. Participants were community-dwelling adult patients already taking a specific drug for hormone replacement (Premarin) or heart conditions (Zestril). They studied the leaflet for their own drug, then participated in multiple

experiments to test all types of information in the leaflet, such as indications (what the drug is used for), precautions, dosage and administration, side effects, and pictograms. The leaflets were generally good in overall design, legibility, and readability.

One of the experiments in this study examined patient knowledge of possible side effects for one of the drugs. The basic Premarin leaflet contained 36 side effects. Most were given in the "side effects" section but some were in the "precautions" section. When asked to report side effects provided throughout the entire leaflet, most participants were unable to report any from the precautions section as shown in Figure 1. Furthermore, performance on items located at the beginning, middle, and end of the side effects section showed the classic serial position effect. Additional testing of information in the "precautions" sections showed that patients did not understand this term well. Thus clustering, chunking, coding, and serial order practices in the leaflet design affected participants' knowledge of the drug's side effects.

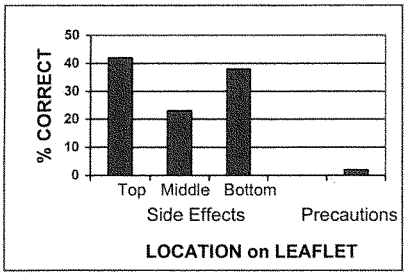

Figure 1 – Knowledge of side effects as a function of their location in a pharmacy leaflet, both for different sections and within the same section.

On a random basis, half the patients were not allowed to see their leaflets during testing (Display-Absent Condition) while the rest were allowed to consult it at any time during the testing phase (Display-Present Condition). The same pattern of results occurred in both conditions, so they were not simply memory effects. Thus leaflet features also affected the ability to search-and-find information when asked for it and to understand it.

These results hold implications for the design of drug information documents. For example, the location of all information must be considered. If there is a well chunked and coded section (such as "side effects"), put all that information in the chunk. If a subset is especially important, locate it at the top of the section. If it must be located elsewhere (such as a boxed warning or precautions section), repeat it in its own section as well. All of these practices can facilitate comprehension, memory, and the ability to find the information again later.

Cognitive Accessibility

Cognitive accessibility is the ease with which people can find, understand, remember, and use information [1]. In the prescription drug setting, the ultimate goals for both healthcare providers and patients are behavioral. Physicians must prescribe appropriate drugs and doses for specific patients and evaluate outcomes accurately, including adverse events. Patients must take a given drug in a safe and effective manner and take appropriate action if side effects occur. Both want to achieve as positive a health outcome as possible. However without sufficient understanding of drug information, such outcomes can be compromised or even prevented.

Analysis of drug information materials provides cognitive accessibility *indicators*, as described above. However it is not until we test materials directly for comprehension, memory, problem solving, and/or other cognitive processes that we have direct evidence about their cognitive accessibility. Nevertheless as findings accumulate, we can make highly accurate predictions about the cognitive consequences of specific materials just from the accessibility indicators themselves.

Cognitive Accessibility of Rx Drug TV Ads

Direct-to-consumer (DTC) advertising of prescription drugs began in earnest in 1997, after a brief previous trial and considerable debate about possible advantages and disadvantages. Previously, drug advertising appeared only in medical journals and other professional materials. Prescription drug promotion now appears in TV ads, magazines, radio, and on the internet (e.g., drug company websites). A major concern is whether consumers understand the potential risks as well as benefits from these materials. In order to study this problem, we developed a large-scale research program on DTC advertising across media (TV, magazines, internet). Below is a sample study on TV ads.

Materials: TV Ads

We have collected drug TV ads since the year 2000 by recording several hours of television a day then extracting whatever ads appeared. Thus we have not selected them for any particular health condition or other factors. We

identify the benefit and risk portions of each ad, perform cognitive accessibility analyses of them, compute cognitive accessibility indices, then compare each ad's treatment of benefits vs. risks. We extract information about many factors, such as the amount and duration of information for benefits vs. risks and language complexity. An example of one type of measure is presented below.

Readability Analysis

We transcribe all spoken information during an ad, both from characters who appear on the screen and from any unseen narrator. We then isolate the language used for benefits vs. risks. To evaluate the comprehensibility of the spoken information, we perform a propositional analyses (e.g., count the number of basic idea units in each sentence), grammatical complexity analyses, and various semantic analyses.

We also compute a readability index. "Readability" is not the same thing as "comprehensibility." Readability indices are generally based on just two factors – word familiarity (frequency of usage in the language) and sentence length (number of words per sentence). They are very simple measures, but easy to compute and are correlated with more sophisticated measures, so we use them as a quick proxy for comprehensibility [12]. A readability score basically shows what reading grade level a person would need to understand some linguistic information. Ordinarily it is used for written language, but can also be applied to spoken language.

In one study [14], we obtained readability scores for 29 Rx drug TV ads, using the Flesch-Kincaid readability index [15]. The drugs were used to treat a variety of indications such as treatment for respiratory allergies, insomnia, arthritis, asthma, migraine, foot fungus, cholesterol reduction, weight loss, birth control, eye irritation, social anxiety disorder, gastric conditions, chemotherapy reactions, flu, and depression.

The average readability scores were higher for side effects than for benefits, as shown in Figure 2. This means that an individual would need only about a 6th grade reading level to understand the benefits in these ads, but a 9th grade level for side effects – three grade levels higher. Most individual drug ads showed this same pattern, with the most extreme case requiring eight additional grade levels to understand its side effects relative to benefits.

Experiment 2 – Cognitive Accessibility of Benefits vs. Risks in TV Ads

To what extent do people understand and remember information about both benefits and risks in Rx drug TV ads? To study this question, we conduct laboratory experiments where people view one or more ad then participate in a battery of cognitive experiments. One type of experiment simply asks them to report the benefits and side effects in the ad. Results from one experiment [17] with three drugs (Paxil, Nasonex, Orthotricyclen) are shown in Figure 3. These results are consistent across many experiments – people are about 80% correct on benefits and only about 20% correct on side effects.

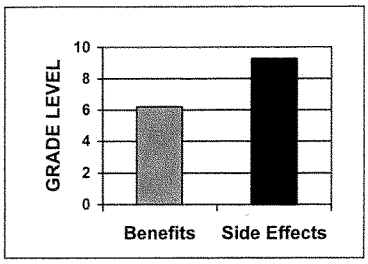

Figure 2 – Readability grade levels of benefits vs. side effects in 29 prescription drug TV ads.

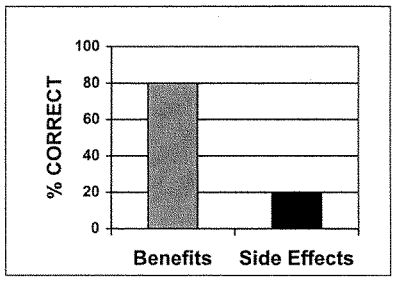

Figure 3 – Percentage correct benefits vs. side effects in an experiment on three prescription drug TV ads.

There are inevitable confounds in experiments using naturalistic materials such as the Original Displays of drug information. For example, existing drug ads generally have more side effects than benefits, so the results shown in Figure 3 could be based at least in part on differences in information load. However performance was comparable when the number of side effects was only three for a given drug (well within the limits of short-term memory) or as many as nine (at or beyond the limits of short-term memory). Therefore different treatment of benefits vs. risks in the ads contributed to the effect. One of the factors

involved was the readability of spoken text, although are others [14, 16].

To study the effects of cognitive accessibility in a more controlled and systematic manner, we also produce our own TV ads for hypothetical drugs. These ads (Enhanced Displays) enable us to control for confounding factors such as the number of benefits vs. risks and test systematically for the effects of other factors.

Alternative Representations

All information can be represented in alternative ways, such as text, lists, and matrices. Each form of representation has cognitive consequences – it can affect cognitive processes such as attention, memory, comprehension, problem solving, and decision making. External representations in hardcopy, electronic, or other means can help shape the mental representation that people develop for a given set of information.

The alternative representations approach [2] takes a given set of information, displays it in alternative formats, then tests for effects on various cognitive processes. No one representation is generally "best." Instead each type may work better for some tasks than others (e.g., search-and-find tasks vs. comprehension tasks) or may facilitate or impede processing of some aspects of the information. Therefore when people have difficulty understanding and using information, the problem may not stem entirely from the nature of the information itself or characteristics of the individual (such as education or motivation). Instead the way the information is displayed may be at least partly responsible, as shown next for medication schedules.

Experiment 3 – Alternative Representations of Medication Schedules

Some patients take multiple prescription drugs, a situation known as polypharmacy. This practice is especially prevalent among older adults. Taking as many as a dozen drugs is not uncommon and some take even more. With so many drugs, medication errors become more likely. For example, patients may forget to take some pills, take too many, or fail to follow restrictions such as taking some with food. Patient medication errors can impede treatment, cause complications, and can lead to hospitalization, increased healthcare expenditures, and even death.

Why do people have difficulty taking their medications? Often the blame is placed on the patients themselves – perhaps they lack knowledge, education, motivation, or sufficient financial resources, or have cognitive deficits. However the way medication instructions are provided may be at least part of the problem.

Materials

Figure 4 shows a medication schedule written by a physician and given to a patient with several health conditions [2]. It is displayed in the commonly used List Format, with the name of each drug and its instructions written on separate lines. This patient had trouble remembering what pills to take, when to take them, and whether he had already taken them.

List

Inderal – 1 tablet 3 times a day

Lanoxin – 1 tablet every a.m.

Carafate – 1 tablet before meals and at bedtime

Zantac – 1 tablet every 12 hours (twice a day)

Quinaglute – 1 tablet 4 times a day

Coumadin – 1 tablet a day

Figure 4 – Medication schedule for an actual patient. It is displayed in the List Format, exactly as written by his physician.

The same medication schedule is reconfigured into the Matrix Format in Figure 5, with the name of the drug along the side, time zones along the top, and checkmarks to indicate when to take each pill. When given the Matrix Format (with the permission of the physician), this patient made no further medication errors.

Matix

	Break-fast	Lunch	Dinner	Bed-time
Lanoxin	✓			
Inderal	✓	✓	✓	
Quinaglute	✓	✓	✓	✓
Carafate	✓	✓	✓	✓
Zantac		✓		✓
Coumadin				✓

Figure 5 – Matrix representations for the same medication schedule shown in Figure 4.

The Matrix solved the compliance problem for this patient in the setting of his everyday life. To examine these alternative representations for medication schedules more systematically, a laboratory experiment was performed [2].

Procedure

During the Study Phase, nonpatient young adults studied the medication schedule shown above. On a random basis, half saw the List Format and half saw the Matrix. They were told that they would see some medication instructions from a doctor to a patient who had been seriously ill, to envision themselves as this patient, and to study the instructions carefully so that they would be able to follow the doctor's orders perfectly.

During the test phase, participants were again asked to envision themselves as the patient taking the medications they had just studied and answered a series of questions. Some of the questions were factual in nature, such as "How many Quinaglute should you take per day?" Others were inferential and required participants to go beyond the explicit information given such as the scenario question, "If you leave home in the afternoon and will not be back until breakfast time the next day, how many Inderal should you take along?"

Participants were assigned randomly to one of two test conditions. For participants in the Display-Absent condition, the study displays were removed, so they had to rely entirely on memory to answer the questions. For those in the Display-Present condition, they kept the same display they had studied and could refer to it throughout the test phase. Thus the experiment used a 2x2 design, with representation (List, Matrix) and test condition (Display-Absent, Display-Present) as the factors and different participants in each of the four resulting groups.

Results and Discussion

Participants who viewed the Matrix performed better than those who viewed the List, as shown in Figure 5. This effect was pronounced for inferential questions, which were more difficult than factual questions. Not surprisingly, performance was worse when participants could not consult the displays during the test phase (Display-Absent), since they had to rely entirely on memory to answer the questions. These participants had no memory load at all – they just had to comprehend and find the information before them. Nevertheless those who used the List performed worse than the Matrix group even when the display was right in front of them, suggesting that this format can impede search and comprehension as well as memory.

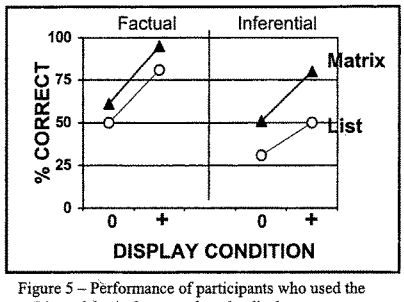

Figure 5 – Performance of participants who used the List or Matrix format, when the display was Absent (0) or Present (+) during testing, for factual vs. inferential test questions.

Curiously, having the List present during testing sometimes provided no benefit. Figure 6 shows results for an inferential question involving a real-world scenario (how many pills to take on a trip given time of departure from home and return later). Although not significant, the downward slope of the list line (from Display-Absent to Display-Present) suggests that being able to view the List may have made matters worse. The possibility that some types of displays are better read and ignored later must be confirmed in future testing with more scenario questions.

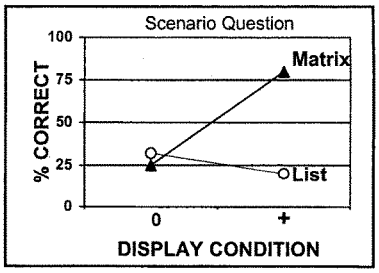

Figure 6 – Performance of participants in the same conditions as shown in Figure 5, for a real-world scenario question.

"Best" Representation. Overall the Matrix was superior to the List for the medication schedule. However the List was still useful in answering factual questions and may be satisfactory for other tasks not tested here, such as remembering the names of the drugs. Thus when we ask which form of representation is "best," we must also ask

"best for what?" The relative success of representational formats may vary depending on the nature of the cognitive task and/or action to be performed. This principle is central to the alternative representations approach [2].

Alternative Representations of Side Effects

The overall format used to display side effects can affect how easily people can understand them, remember them, and know what actions to take if they occur. Below are some alternative representations for the same set of side effects for a hypothetical drug. The example is used to illustrate just some of the possible ways to display side effects. Results from laboratory experiments on these and other alternative displays are provided in [17].

Paragraph Format

A typical way to represent side effects is in paragraph form, which is widely used in both patient and professional information sources. Even within this traditional format, there are alternative versions, as shown in Figure 7. The Plain Paragraph just strings out the side effects, without categorizing them in any way. It also introduces them with the neutral term "include" that provides no information about their severity or likelihood of occurrence.

The Categorized Paragraph chunks and codes side effects using the severity terms "dangerous," "worrisome," and "mild." They could also be categorized by frequency terms such as "more common," "less common," and "rare." (*Note:* the use of the severity and frequency terms in this example is not a recommendation that they "should" be used; for research on how people perceive these and other terms, see [18, 19]). Although the Categorized Paragraph adds descriptor terms and syntactic structures to cluster subsets of side effects together, it still looks like the Plain Paragraph. It does not provide distinctive visual cues for the semantic categories it provides. Additional enhancements could do so, such as underlining the descriptor terms.

Plain Paragraph

Possible side effects include chest pain, slurred speech, seizure, anxiety, joint pain, weakness, dry mouth, headache, and nausea.

Categorized Paragraph

Possible dangerous side effects include chest pain, slurred speech, and seizure. Some are worrisome such as anxiety, joint pain, and weakness while others are generally mild such as dry mouth, headache, and nausea.

Figure 7 – Alternative versions of the Paragraph Format for representing the same side effects.

List Format

The same set of side effects is also shown in the List Format (Figure 8). The Plain List makes it easier to see about how many side effects there are overall. This is useful information for comparing side effect profiles across drugs and for knowing about how many to watch for during the course of treatment. It may also facilitate remembering which side effects are possible.

The Chunked List goes beyond just categorizing the side effects by severity (as in the Categorized Paragraph), since it also separates the severity groups with blankspace. This particular version also makes the descriptor terms more visually distinctive (different font style, larger font size, bolded, underlined).

Plain List	Chunked List
--chest pain --slurred speech --seizure --anxiety --joint pain --weakness --dry mouth --headache --nausea	**Dangerous** --chest pain --slurred speech --seizure **Worrisome** --anxiety --joint pain --weakness **Mild** --dry mouth --headache --nausea

Figure 8 – Alternative versions of the Paragraph Format for representing the same side effects.

Line Format

Linear order diagrams show how items vary along a single dimension such as severity or frequency. One type of linear diagram is the simple Line Format as shown in Figure 9. It emphasizes various aspects of the information including the similarities and differences in severity among items; the relative number of items in each chunk; and the degree of severity for each set chunk. It also can reduce the number of category names needed to just the high and low anchor points.

Line

Mild		Dangerous
dry mouth	anxiety	chest pain
headache	joint pain	tingling
nausea	weakness	seizure

Figure 9 – Line Format for representing the severity (or frequency) of side effects.

Arrow Format

The Arrow Format also provides linear order, as shown in Figure 10. The arrow emphasizes the increasing magnitude of severity and directs attention to the most severe side effects. Other optional enhancements include larger bold characters for the most severe items and smaller italicized characters for the mild ones (such enhancements can be used in other formats as well). The anchor points can be either linguistic as shown for the Line Format in Figure 9, or pictorial as shown for the Arrow.

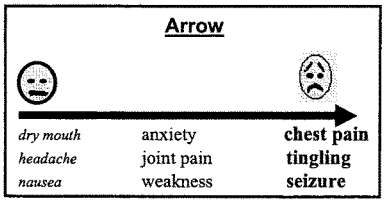

Figure 10 – Arrow Format for representing the severity (or frequency) of side effects.

Pictograms can add interest and might help people with lower literacy levels. However, comprehension testing is essential before using them. Even well known symbols can be misinterpreted. For example, when we showed a standard pictogram with a pregnant woman and a question mark intended to mean "Are you pregnant…?" participants gave multiple interpretations including, "She's wondering whether to tell her boyfriend" [13].

Matrix Format

Two major dimensions underlie side effects – severity and frequency of occurrence. The Matrix Format displays both types of information, as shown in Figure 11. For simplicity, only two semantic categories are displayed for each dimension. Note that the descriptor terms for each dimension are just examples; for cautions about using specific severity and frequency terms, see [18].) An advantage of the Matrix is that it can show empty cells – in this case, showing that dangerous side effects are rare.

Matrix

	Dangerous	Mild
Common		dry mouth
Rare	chest pain tingling seizure	headache nausea

Figure 11 – Matrix Format for representing both severity and frequency of side effects.

Other Formats

We have developed and tested other types of formats for representing side effects, in addition to those shown here. All have advantages over the Plain Paragraph, although some are better than others. The percentage increase in performance from Original to Enhanced Displays can be dramatic – from 80% to 800% in some cases [17].

General Discussion and Implications

Cognitive Accessibility

Experiments using Original Displays of drug information show that poor cognitive accessibility of information is a major contributor to poor comprehension. Also, performance on risks is significantly worse across a wide range of materials and cognitive tasks. The problem is not simply that people find risks "scary," since when we repeat experiments with the same risks using Enhanced Displays, performance improves, often dramatically.

Cognitive accessibility must be considered for all types of drug information, especially risks. Otherwise materials may meet regulatory and legal criteria for "providing" risk information, yet fail to communicate it. Therefore this work reveals an important principle:

> Information can be physically present yet functionally absent.

Alternative Representations

An unlimited number of alternative representations can be generated. However "fixing" one problem with a new design may make something else worse. Therefore it is important to design new representations based on cognitive principles and evaluate them in comprehension testing.

Participants

The basic results reported here for laypersons occur across a wide range of demographic factors, including age and education level [13]. Although younger and more educated people may have higher overall performance scores on some tasks, they still show the *same pattern* of results – poor performance on risks but significant improvement with Enhanced Displays.

Healthcare professionals should do better overall than laypersons in these types of experiments, and they do. Nevertheless they still show the *same pattern* of results – poor performance on risks relative to benefits but improvement with Enhanced Displays. Despite their substantial knowledge about prescription drugs they are still human, with the same basic cognitive processes as others. They too can be overloaded, have trouble using

documents with low cognitive accessibility, and can miss or misunderstand some of the information.

Health Outcomes

Relying on information sources with poor cognitive accessibility can decrease the effectiveness of drug treatment and increase the probability of medical error. For example, a physician may not find or remember a specific drug-drug interaction in the *Physicians Desk Reference* and prescribe a drug that interacts negatively with one a patient is already taking. Although electronic prescribing technology can reduce this type of error, it does not eliminate it. The way information is provided in any medium can contribute to errors.

Patients also need to understand risks as well as benefits. It can affect their compliance with instructions and their knowledge of what to do if side effects occur. Therefore enhancing the cognitive accessibility of risks is also critical for laypersons to achieve good health outcomes.

Interdisciplinary Research

Although based primarily on cognitive principles and methods, this research is interdisciplinary in nature. It uses concepts and perspectives from linguistics, cognitive science, computer science, medicine, pharmacy, and public policy. For example, issues common to cognitive science and artificial intelligence include representation, the nature of expertise, and the design and use of intelligent systems. This work also provides a testbed for studying cross-discipline concepts in the context of a real-world setting.

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United States Government Accountability Office

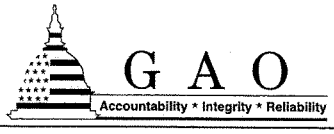
GAO

Report to Congressional Requesters

November 2006

PRESCRIPTION DRUGS

Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising



GAO-07-54

GAO
Accountability·Integrity·Reliability

Highlights

Highlights of GAO-07-54, a report to congressional requesters

November 2006

PRESCRIPTION DRUGS

Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising

Why GAO Did This Study

The Food and Drug Administration (FDA) is responsible for overseeing direct-to-consumer (DTC) advertising of prescription drugs. If FDA identifies a violation of laws or regulations in a DTC advertising material, the agency may issue a regulatory letter asking the drug company to take specific actions. GAO was asked to discuss (1) trends in drug company spending on DTC advertising and other activities; (2) what is known about the relationship between DTC advertising and drug spending and utilization; (3) the DTC advertising materials FDA reviews; (4) the number of regulatory letters that cited DTC materials and FDA's process for issuing those letters; and (5) the effectiveness of these letters at limiting the dissemination of violative DTC advertising. GAO reviewed research literature, analyzed FDA's processes, and examined FDA documentation.

What GAO Recommends

GAO recommends that FDA (1) document criteria for prioritizing DTC materials for review, (2) systematically apply its criteria to materials it receives, and (3) track which materials it reviews. In its comments on a draft of this report, HHS disagreed with the recommendations, stating that they would require vastly increased staff. GAO believes that FDA already has most of the information that would be required to establish a systematic process for screening DTC materials.

www.gao.gov/cgi-bin/getrpt?GAO-07-54

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse at (202) 512-7119 or crossem@gao.gov.

What GAO Found

Drug company spending on DTC advertising—such as that on television and in magazines—of prescription drugs increased twice as fast from 1997 through 2005 as spending on promotion to physicians or on research and development. Over this period, drug companies spent less each year on DTC advertising ($4.2 billion in 2005) than on promotion to physicians ($7.2 billion in 2005) or research and development ($31.4 billion in 2005).

Studies GAO reviewed suggest that DTC advertising has contributed to increases in drug spending and utilization, for example, by prompting consumers to request the advertised drugs from their physicians, who are generally responsive to these requests. Evidence suggests that the effect of DTC advertising on consumers can be both positive, such as encouraging them to talk to their doctors, and negative, such as increased use of advertised drugs when alternatives may be more appropriate.

FDA reviews a small portion of the DTC materials it receives. To identify materials that have the greatest potential to impact public health, FDA has informal criteria to prioritize materials for review. However, FDA has not documented these criteria, does not apply them systematically to all of the materials it receives, and does not track information on its reviews. As a result, the agency cannot ensure that it is identifying or reviewing those materials that it would consider to be the highest priority.

FDA has taken longer to draft and review regulatory letters and the agency has issued fewer letters per year since 2002, when legal review of all draft regulatory letters was first required. From 2002 through 2005, from the time FDA began drafting a regulatory letter for a violative DTC material, it took the agency an average of 4 months to issue a regulatory letter, compared with an average of 2 weeks from 1997 through 2001. FDA has issued about half as many regulatory letters per year since the 2002 policy change.

The effectiveness of FDA's regulatory letters at halting the dissemination of violative DTC materials has been limited. The 19 regulatory letters FDA issued in 2004 and 2005 were issued an average of 8 months after the materials were first disseminated. By the time FDA issued these letters, companies had already discontinued use of more than half of the violative materials. When the cited materials were still being disseminated, drug companies complied with FDA's requests to remove the materials, and identified and removed other materials with similar claims. FDA's issuance of regulatory letters did not always prevent drug companies from later disseminating similar violative materials for the same drugs. These issues are not new. In 2002, GAO reported that, by delaying the issuance of regulatory letters, the 2002 policy change had adversely affected FDA's ability to enforce compliance. At that time, GAO recommended, and FDA agreed, that letters be issued more quickly. GAO continues to believe this is necessary in order to limit consumers' exposure to false or misleading advertising.

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Abbreviations

DDMAC	Division of Drug Marketing, Advertising, and Communications
DTC	direct-to-consumer
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
OCC	Office of the Chief Counsel
PhRMA	Pharmaceutical Research and Manufacturers of America

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HARVARD
School of Public Health

Summary and Chartpack

USA Today/Kaiser Family Foundation/Harvard School of Public Health

The Public on Prescription Drugs and Pharmaceutical Companies

March 2008

Methodology

The *USA Today*/Kaiser Family Foundation/Harvard School of Public Health Survey Project is a three-way partnership. *USA Today*, Kaiser, and the Harvard School of Public Health jointly design and analyze surveys examining health care issues.

Representatives of *USA Today*, The Henry J. Kaiser Family Foundation, and the Harvard School of Public Health worked together to develop the survey questionnaire and analyze the results. *USA Today* retains editorial control over the content published by the paper. The project team included Jim Norman, USA Today polling editor; Drew E. Altman, president of the Kaiser Family Foundation, Mollyann Brodie, vice president and director of public opinion and media research, and Liz Hamel, associate director of public opinion and media research; and Robert J. Blendon, professor of health policy and political analysis at the Harvard School of Public Health and the John F. Kennedy School of Government, and John M. Benson, managing director of the Harvard Opinion Research Program in the Harvard School of Public Health.

The Public on Prescription Drugs and Pharmaceutical Companies is a nationally representative, random sample survey of 1,695 adults ages 18 years and older. The survey was conducted by telephone from January 3-23, 2008. Telephone interviews were carried out in English and Spanish by ICR/International Communications Research of Media, PA.

The margin of sampling error for the survey is plus or minus 3 percentage points for total respondents. For results based on smaller subsets of respondents the margin of sampling error is higher. Sampling error is only one of many potential sources of error in this or any other public opinion poll.

Values less than 0.5% are indicated by an asterisk (*). "Vol." indicates that a response was volunteered by respondent, not an explicitly offered choice. Percentages may not always add up to 100% due to rounding.

KEY FINDINGS

Key finding #1: Americans love the products that pharmaceutical companies produce, but they are less favorable towards the companies themselves, mainly because they feel they are getting ripped off by high prices driven by high drug company profits.

While a plurality (47%) of the public says they have a favorable view of pharmaceutical companies, more than four in ten (44%) have an unfavorable view of these companies, outranked only by health insurance companies (54%) and oil companies (63%) (Chart 1).

Despite these mixes views of pharmaceutical companies, the public has positive views towards prescription drugs in general, and even has some nice things to say about the companies that make them. Nearly three-quarters (73%) say prescription drugs developed over the past 20 years have made the lives of people in the U.S. better (including 52% who say "a lot" better), and nearly two-thirds (63%) say the same about their own and their family members' lives. Very few say prescription drugs have made Americans' lives (10%) or their own lives (4%) worse (Chart 2).

Among those with a favorable opinion of drug companies, when asked why their opinion is favorable, about two-thirds (64%) mention the quality and/or importance of the products and research provided by the industry (Chart 3). However, people don't necessarily see drug companies standing out from other types of companies because of the work that they do. Just about a quarter (26%) of the public believes that, by researching and developing new drugs, pharmaceutical companies make more of a contribution to society than most other companies, while more than half (56%) say their contribution is about the same (Chart 4).

On the other hand, the high cost of drugs and high profits made by drug companies are Americans' biggest beef with the pharmaceutical industry. Among those with an unfavorable opinion of drug companies, when asked why their opinion is unfavorable, two-thirds (68%) give responses related to high prices, high profits, or company greed (Chart 5).

Negative opinions about drug prices and drug company profits are not limited to those with an unfavorable view of pharmaceutical companies. Among all Americans, eight in ten (79%) say the cost of prescription drugs is unreasonable (Chart 6), and seven in ten (70%) say pharmaceutical companies are too concerned about making profits and not concerned enough about helping people (Chart 7). Profits made by pharmaceutical companies are also seen as the biggest driver of the cost of drugs (79% say this is a "major" factor, compared with 72% for the cost of medical research, 62% for the cost of advertising, and 56% for the cost of lawsuits) (Chart 8). And while most people trust pharmaceutical companies at least "somewhat" when it comes to developing new drugs and providing reliable information, six in ten (58%) do *not* trust pharmaceutical companies to price their products fairly (Chart 9).

Americans' anger over the cost of prescription drugs may stem at least in part from a sense that they are being charged unfairly compared to people in other countries. Three-quarters (76%) of the public thinks that people in the U.S. pay higher prices for the same prescription drugs than people in Canada, Mexico, and Western Europe (Chart 10).

Further evidence that high prices and profits are the biggest negative in people's views of the pharmaceutical industry comes from responses to questions about government regulation. While pluralities say there is about the right amount of regulation when it comes to drug safety (47%) and making sure prescription drug advertisements are not misleading (48%), nearly two-thirds (64%) say there is *not enough* regulation when it comes to limiting the price of prescription drugs (Chart 11). Even when presented with the argument that price regulation could lead to less research and development on new drugs, nearly half (48%) say there should be more regulation in this area (Chart 12).
Despite these negative views of prescription drug prices overall, many people do recognize a role for prescription drugs in keeping down the overall cost of health care; six in ten (59%) say prescription drugs reduce the need for expensive medical procedures and hospitalizations, and nearly as many (56%) say prescription drugs reduce health care costs by preventing illnesses (Chart 13).

The amount and content of prescription drug advertising is often attacked by critics of the pharmaceutical industry. However, this survey finds that, while the public does express some negative views about advertising, these views plays less of a role in people's negative views of the industry compared with high prices and profits. More than half the public (53%) say prescription drug advertising is mostly a good thing, and two-thirds (67%) agree that these ads educate people about treatments and encourage them to get help for conditions they might not have been aware of (Chart 14).

On the negative side, people's biggest beef with advertising again comes back to cost; more than three-quarters say the cost of advertising makes prescription drugs too expensive, and four in ten say this bothers them "a lot." While about two-thirds say there are too many prescription drug ads on television (68%) and that ads encourage people to take medications they don't need (66%), fewer say they are bothered "a lot" by either of these issues (27% and 34%, respectively). Nearly half the public (46%) thinks that many prescription drug ads are too sexually explicit, but just one in five (20%) say this bothers them a lot (Chart 15).

Negatives of prescription drug ads	**% who agree with each**	**% who say each bothers them "a lot"**
The cost of ads makes drugs too expensive	77%	41%
Ads encourage people to take drugs they don't need	66	34
There are too many drug ads on television	68	27
Many ads are too sexually explicit	46	20

Key finding #2: Significant shares of people are having difficulty paying for prescription drugs, and many have not filled prescriptions, skipped doses, or cut pills in half as a result.

More than half (54%) of Americans say they currently take prescription medicines, including 50% who take them daily. One in five (19%) say they are currently taking four or more prescription drugs (Chart 18). Not surprisingly, prescription drug use is more common among the elderly (42% currently take four or more drugs) and those in fair or poor health (46% take four or more drugs).

Significant shares report difficulty affording the drugs they need. Four in ten adults (41%) say it is at least somewhat of a problem for their family to pay for prescription drugs they need, including 16% who say it is a serious problem (Chart 19). Three in ten (29%) say that in the last two years, they have not filled a prescription because of the cost, and nearly a quarter (23%) say they have cut pills in half or skipped doses in order to make a medication last longer. Four in ten report at least one of these three problems (a serious problem paying for drugs, not filling a prescription because of cost, and/or skipping doses in the past two years) (Chart 20).

Problems paying for prescription drugs, not filling prescriptions because of cost, and skipping doses are even more common among those who take larger numbers of prescription drugs, those who don't have insurance to cover their prescription drug costs, and those with lower incomes (Chart 21).

	Public overall	**Currently take any Rx**	**Currently take 4+ Rx drugs**	**No insurance to pay for Rx**	**Income <$25K**
It's a SERIOUS problem for you and your family to pay for Rx drugs you need	16%	19%	27%	32%	29%
In last 2 years, have not filled a prescription because of cost	29	36	41	39	40
In last 2 years, have skipped doses or cut pills in half to make Rx last long	23	34	39	27	31
Percent reporting at least one of above three problems	40	50	59	52	54

While many people report problems paying for drugs, there is at least some awareness of pharmaceutical company programs to provide free or discounted drugs to people who cannot afford them. Nearly six in ten adults (58%) have heard of these programs, but two-thirds (65%) of those who have heard of them think the programs don't go far enough to help people who need them (Chart 22). About one in six people (16%) say that they or someone in their family has ever applied for discount or free medications from a pharmaceutical company.

Key finding #3: Prescription drug advertising has driven a third of Americans to talk to their doctors about specific prescription drugs, and many of these people got a prescription from their doctor as a result.

Almost all Americans (91%) have seen or heard prescription drug ads, and nearly a third (32%) have talked to a doctor about a prescription drug they saw advertised (Chart 23). Among those who have talked to a doctor about a drug they saw advertised, 44% say their doctor gave them a prescription for the drug they asked about, and 54% say their doctor recommended another prescription drug (resulting in 82% who got a prescription either for the drug they asked about and/or another drug) (Chart 24).

As mentioned previously, people's views of prescription drug ads are mainly positive. Slim majorities of adults overall say drug ads do an excellent or good job telling people about the potential benefits of a medication (56%) and the condition a drug is designed to treat (54%), but a similar share (53%) say these ads do only a fair or poor job telling people about the potential side effects of the drug (Chart 25).

Six in ten (60%) think ads for medications to treat mental health conditions are mostly good because they improve understanding of these conditions and encourage people to seek treatment, while about a third (36%) think these ads are mostly bad because they encourage people without serious mental health conditions to think they need treatment (Chart 26).

Key finding #4: Despite recent controversies about how pharmaceutical companies test drugs, the majority of Americans believe these companies do enough to test and monitor the safety of their drugs and that they conduct these tests in an ethical way. A majority also believes that drug companies do not have too much influence over which drugs are approved by the FDA, another issue that has been in the news. However, in each of these areas, a substantially minority has a negative view.

Nearly eight in ten Americans (78%) are at least somewhat confident that prescription drugs sold in the U.S. are safe, though just over a quarter (27%) are "very" confident. About half (49%) think drugs manufactured in other countries and sold in the U.S. are about as safe as those made here, but a notable four in ten (41%) think they are less safe (Chart 27).

Despite recent controversies, over half the public (55%) thinks pharmaceutical companies do enough to test and monitor the safety of their drugs (Chart 28), and the same share (55%) trust pharmaceutical companies at least somewhat to quickly notify the public about safety concerns (Chart 9). Majorities also think that pharmaceutical companies act in an ethical way when testing their products on people (62%) and on animals (56%) (Chart 29). However, substantial minorities hold negative views in these areas: four in ten (41%) think pharmaceutical companies *do not* do enough to test and monitor the safety of their products; 44% do not trust companies to notify the public quickly about safety concerns; and about three in ten think most pharmaceutical companies act unethically when testing their drugs on people (28%) and animals (30%).

When it comes to the drug review and approval process, most people do not think pharmaceutical companies have too much influence over the FDA, and a majority would like to see the government move more quickly when approving new drugs. About half (51%) say that pharmaceutical companies have too little or the right amount of influence on which drugs are approved by the FDA, compared with about four in ten (42%) who say these companies have too much influence (Chart 30). More than half (52%) say the government moves too slowly when reviewing and approving new drugs (Chart 31).

Key finding #5: Americans are divided over who should have primary responsibility for developing new drugs, seeing a role for drug companies, universities, and the federal government.

Pharmaceutical companies are seen as playing the biggest role currently in researching and developing new drugs. However, the public is split when it comes to who *should* be primarily responsible for developing new drugs, with roughly equal shares saying pharmaceutical companies (28%) and universities (27%), and somewhat smaller shares choosing the federal government (16%) and non-profit organizations (11%) (Chart 32).

	% who think each play a major role in researching and developing new drugs	% who say each SHOULD be primarily responsible for developing new drugs
Pharmaceutical companies	75%	28%
Universities	60	27
Federal government	49	16
Non-profit organizations	24	11
Some combination		13

When it comes to the more difficult issues of "orphan drugs" (those to treat diseases that affect a relatively small number of people) and drugs for people in poorer countries, the majority of Americans do not believe that drug companies should have the main responsibility for making sure research is conducted. When it comes to orphan drugs, nearly half (48%) say the federal government should take responsibility for research (compared with 27% who say pharmaceutical companies). Similarly, when it comes to drugs for diseases that mostly affect people in poorer countries around the world, four in ten (42%) place the responsibility on international non-profits (compared with 19% for pharmaceutical companies) (Chart 33).

ADDITIONAL FINDINGS

Sources of information and talking to doctors

Doctors rank number one in terms of the sources people rely on for information about prescription drugs. More than seven in ten (72%) say they rely on their doctor "a lot" to provide accurate information about prescription medicines, compared with 51% for their pharmacist, 43% for the information contained in drug product packaging, 22% for government agencies like the FDA, and 15% for family and friends (Chart 34).

However, when it comes to the cost of drugs, people are more likely to talk to their pharmacist than their doctor. Fewer than half (44%) say they usually talk to their doctor about the cost of a drug when they get a new prescription, but 61% say they usually talk to their pharmacist about whether cheaper alternatives are available when filling a prescription (Chart 35). A few groups are more likely to say they usually talk to their doctor about the cost of their medications, including those who say paying for drugs is a serious problem for their family (64%), those who have applied for a pharmaceutical company discount (64%), those who do not have insurance to help pay for drugs (56%), and those with incomes less than $25,000 a year (57%).

Proving effectiveness of new drugs compared to existing treatments

On the question of whether new drugs should be approved only if they are proven to be more effective than existing treatments, more than half think the FDA should make decisions based only on whether drugs are safe and effective. However, nearly six in ten say insurance companies should only pay for new drugs if they have been proven to be more effective than existing alternatives (Chart 36).

	FDA should approve new drugs...	Insurance companies should pay for new drugs...
Only if they are proven to be more effective than existing treatments	44%	**58%**
Regardless of whether they are proven to be more effective than existing treatments	**53**	38

More on those with favorable and unfavorable opinions of pharmaceutical companies

While the public overall is somewhat split between having a favorable (47%) and an unfavorable (44%) opinion of pharmaceutical companies, some groups express different levels of favorability than others. Groups who have the highest share saying they have a favorable opinion of drug companies include Hispanics (63% favorable), those who have applied for drug company discounts (56%), Republicans (56%), those with a household income less than $25,000 (55%), those with a high school education or less (52%), and people who live in the suburbs (51%). Groups with the highest share expressing an *unfavorable* opinion of drug companies include those with household incomes between $50,000 and $75,000 (54%), college graduates (51%), people who live in rural areas (51%), those with household incomes of $75,000 or more (49%), and non-Hispanic whites (48%).

Those who have an unfavorable opinion of pharmaceutical companies are more likely than those with a favorable opinion to express a variety of negative views, particularly when it comes to pharmaceutical company profits and prices, and the amount of influence drug companies have over various government processes.

However, there are some areas where even majorities of those who have unfavorable opinions of drug companies express positive views of these companies or of the drugs themselves. For instance, two-thirds (66%) of those with an unfavorable view of pharmaceutical companies say that prescription drugs developed over the past 20 years have made the lives of people in the U.S. better, and over half (53%) say the same about their own and their family members' lives. Majorities of this group also believe that most pharmaceutical companies engage in ethical testing practices when they test their drugs on people (56%) and animals (53%). More than two-thirds (68%) of those with an unfavorable view of drug companies are at least somewhat confident that prescription drugs sold in the U.S. are safe, and majorities trust pharmaceutical companies at least somewhat to offer reliable information about their products and to develop new, effective drugs.

	Opinion of drug companies	
	Favorable (48% of public overall)	**Unfavorable (44% of public overall)**
Pharmaceutical companies are too concerned about making profits, and not concerned enough about helping people	54%	86%
Rx drug costs are unreasonable	65	94
Rx drug advertising is mostly a bad thing	27	56
Pharmaceutical companies have too much influence on…		
…which drugs are approved by the FDA	28	57
…laws and regulations passed by Congress	38	66
…efforts to change the health care system in the U.S.	30	61
Trust pharmaceutical companies a lot/somewhat to…		
…offer reliable information about how well their drugs work	79	61
…offer reliable information about side effects and safety of their drugs	82	62
…develop new, effective drugs	85	73
Rx drugs developed over past 20 years have made lives of people in U.S. better	81	66
Rx drugs developed over past 20 years have made your/family's lives better	74	53
Very/somewhat confident that Rx drugs sold in the U.S. are safe	89	68
Most pharmaceutical companies act in an ethical way when researching and testing new drugs on people	70	56
Most pharmaceutical companies act in an ethical way when researching and testing new drugs on animals	62	53

Experiences and opinions of people with lower incomes

Being older and in poorer health, lower-income people are more likely to take prescription drugs, and regularly take more prescriptions than their higher-income counterparts. Nearly a third (32%) of people in households earning less than $25,000 a year say they currently take four or more prescription drugs, compared with 12% of those earning $75,000 or more.

Not surprisingly, those with lower incomes are also more likely to have serious problems paying for medications, and to say that in the past two years, they have not filled prescriptions because of the cost and/or skipped doses to make a medication last longer. Fully four in ten people with incomes less than $25,000 report not filling a prescription in the past two years because of cost, compared with fewer than two in ten (18%) of those with incomes of $75,000 or more. At least some of these problems may stem from the fact that lower-income people are less likely to have insurance coverage for prescription drugs (63% of those earning less than $25,000 report having coverage, compared with 95% of those earning $75,000 or more). Lower-income people are also more likely to say they talk to their doctors about the cost of prescriptions, and that they have applied for drug company discounts.

Despite having more difficulty paying for prescriptions, people with incomes less than $25,000 are somewhat more likely to have a favorable opinion of drug companies (55%, compared with 44% of those with incomes of $25,000 or more), and express somewhat less negative views of drug company profits, prices, marketing and advertising. For instance, 66% of those with incomes less than $25,000 say that pharmaceutical companies are too concerned about making profits and not concerned enough about helping people, compared with 74% of those with higher incomes. And while more than half (55%) of people with incomes over $25,000 think pharmaceutical companies spend too much money marketing to doctors, just 38% of people with lower incomes share this view.

However, in a few areas, lower-income people express slightly more negative views than their higher-income counterparts. For example, people with lower incomes are somewhat less likely to say prescription drugs developed over the past 20 years have made Americans' lives better, and somewhat *more* likely to think most pharmaceutical companies engage in unethical testing practices.

	Household income			
	<$25K	**$25-49K**	**$50-74K**	**$75K+**
Age 65+	25%	17%	11%	6%
Health status is fair or poor	43	20	11	5
Have a disability or chronic disease that keeps from participating in daily activities	39	20	16	9
Currently take any Rx drugs	64	53	56	48
...take 4 or more Rx drugs	32	17	14	12
Serious problem for you and your family to pay for drugs	29	19	13	5
Last 2 years, ever not filled a prescription because of the cost	40	33	28	18
Last 2 years, ever skipped doses or cut pills in half	31	28	19	14
Have insurance that helps pay for drugs	63	78	88	95
Usually talk to doctor about cost of medicine	57	47	37	34
Self or family member ever applied for a discount from a pharmaceutical company	29	15	13	8
Favorable view of pharmaceutical companies	55	46	36	46
Cost of Rx drugs is unreasonable	72	87	87	78
Pharmaceutical companies are too concerned about making profits, and not concerned enough about helping people	66	71	80	71
Rx drug advertising is mostly a good thing	59	55	43	48
Pharmaceutical companies spend too much money advertising to patients	52	54	70	67
Pharmaceutical companies spend too much money on marketing to doctors	38	54	58	56
Rx drugs developed over past 20 years have made lives of people in U.S. better	66	68	77	82
Most pharmaceutical companies engage in testing practices that are unethical and put people at risk	40	34	27	20

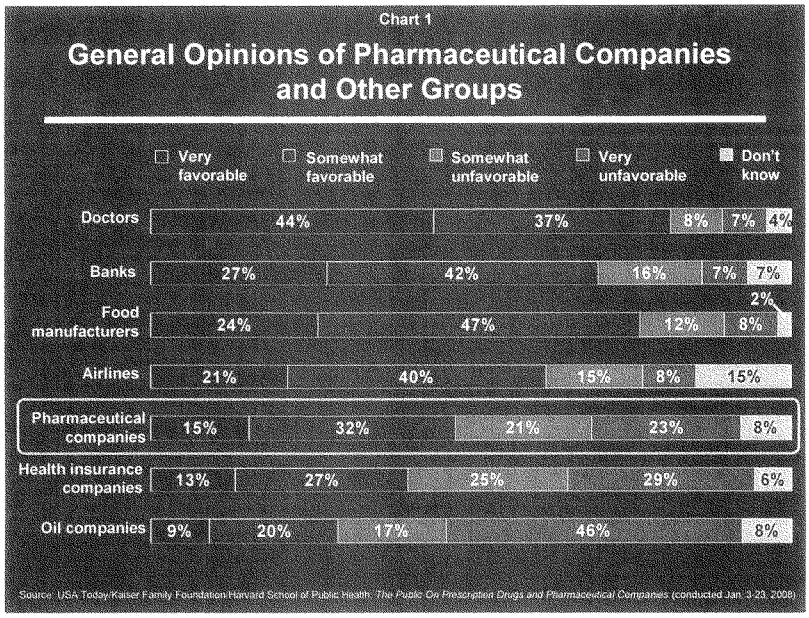


Chart 1
General Opinions of Pharmaceutical Companies and Other Groups
Very favorable
Somewhat favorable
Somewhat unfavorable
Very unfavorable
Don't know
Doctors
44%
37%
8%
7%
4%
Banks
27%
42%
16%
7%
7%
Food manufacturers
24%
47%
12%
8%
2%
Airlines
21%
40%
15%
8%
15%
Pharmaceutical companies
15%
32%
21%
23%
8%
Health insurance companies
13%
27%
25%
29%
6%
Oil companies
9%
20%
17%
46%
8%
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

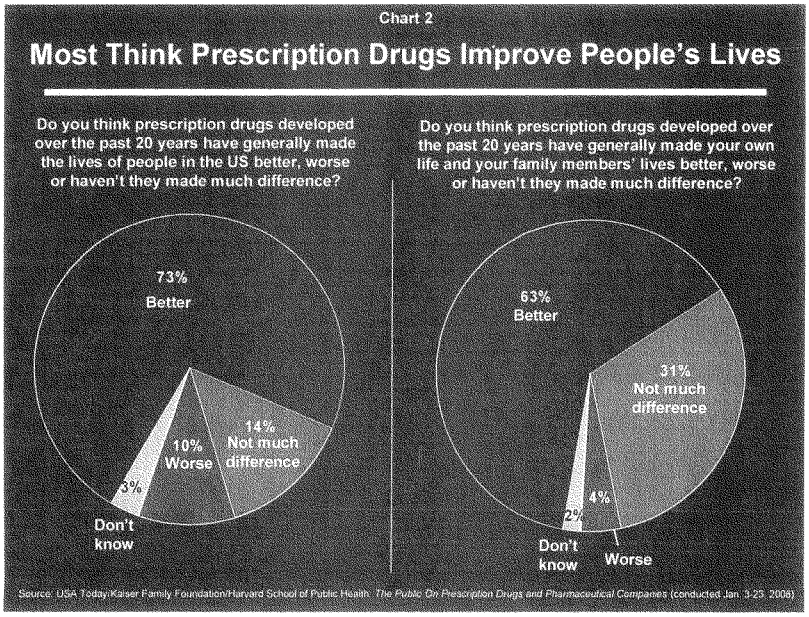


Chart 2
Most Think Prescription Drugs Improve People's Lives
Do you think prescription drugs developed over the past 20 years have generally made the lives of people in the US better, worse or haven't they made much difference?
73%
Better
14%
Not much difference
10%
Worse
3%
Don't know
Do you think prescription drugs developed over the past 20 years have generally made your own life and your family members' lives better, worse or haven't they made much difference?
63%
Better
31%
Not much difference
4%
2%
Don't know
Worse
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

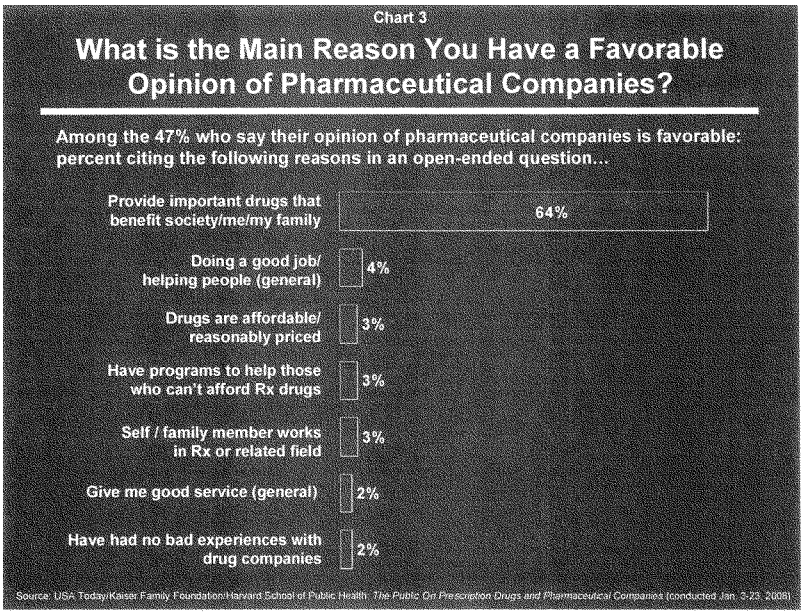


Chart 3
What is the Main Reason You Have a Favorable Opinion of Pharmaceutical Companies?
Among the 47% who say their opinion of pharmaceutical companies is favorable: percent citing the following reasons in an open-ended question...
Provide important drugs that benefit society/me/my family
64%
Doing a good job/ helping people (general)
4%
Drugs are affordable/ reasonably priced
3%
Have programs to help those who can't afford Rx drugs
3%
Self / family member works in Rx or related field
3%
Give me good service (general)
2%
Have had no bad experiences with drug companies
2%
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

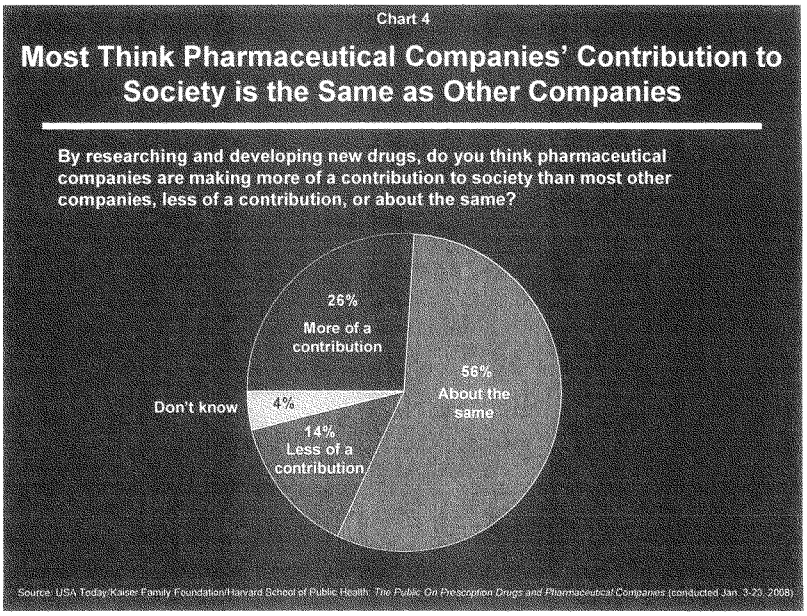
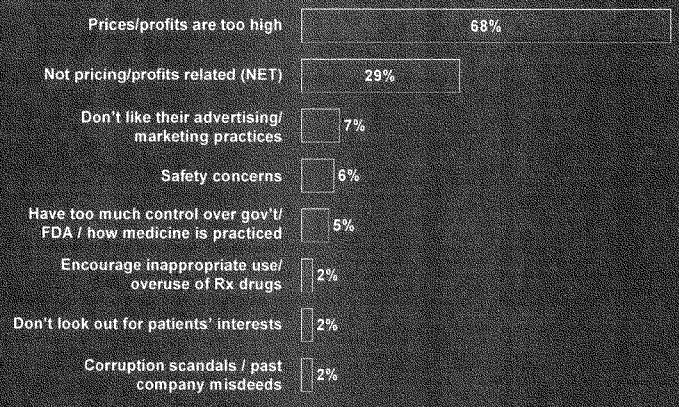


Chart 4
Most Think Pharmaceutical Companies' Contribution to Society is the Same as Other Companies
By researching and developing new drugs, do you think pharmaceutical companies are making more of a contribution to society than most other companies, less of a contribution, or about the same?
26%
More of a contribution
56%
About the same
Don't know
4%
14%
Less of a contribution
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

Chart 5

What is the Main Reason you Have an Unfavorable Opinion of Pharmaceutical Companies?

Among the 44% who say their opinion of pharmaceutical companies is unfavorable: percent citing the following reasons in an open-ended question...

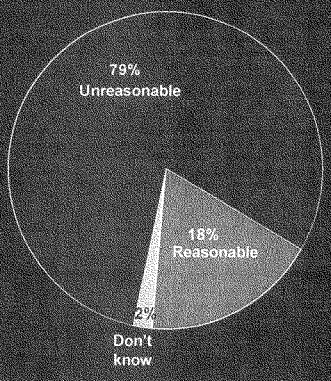


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

Chart 6

Most Say Prescription Drug Cost is Unreasonable

In general, do you think the cost of prescription drugs is reasonable or unreasonable?

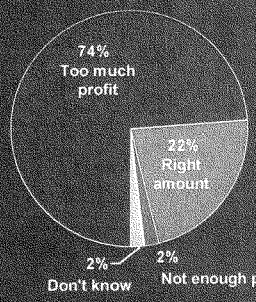


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

Chart 7

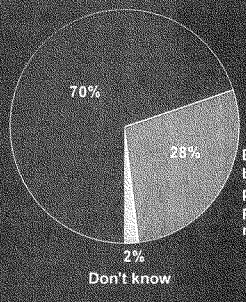
Many Believe Drug Companies Too Concerned with Profit

In general, do you think pharmaceutical or drug companies make too much profit, not enough profit, or about the right amount of profit?



Which statement comes closer to your view?

Drug companies are too concerned about profits, not concerned enough about helping people



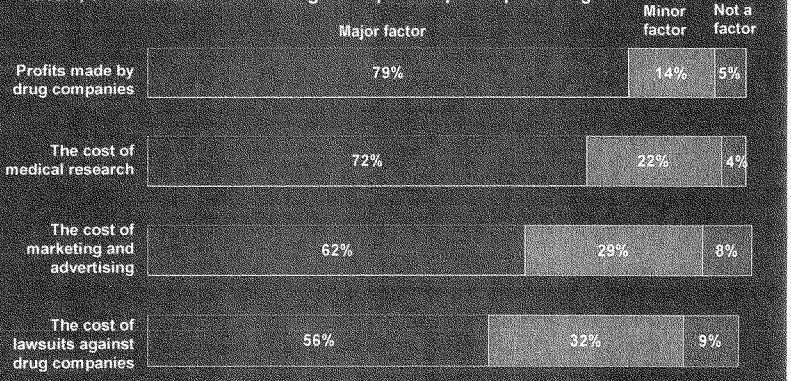
Balance of concern between making profits and helping people is about right

Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

Chart 8

Profits Seen As the Biggest Driver of Price of Prescription Drugs

I'm going to read you some factors that some people say contribute to the price of prescription drugs. For each, I'd like you to tell me if this is a major factor, a minor factor, or not a factor contributing to the price of prescription drugs.



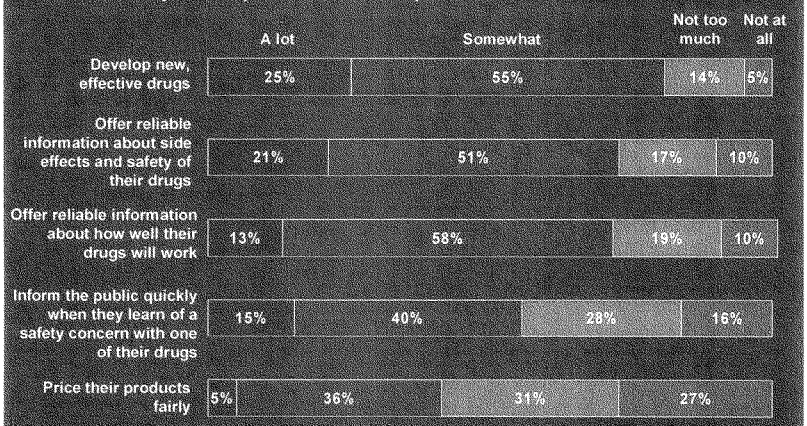
Note: "Don't know" responses not shown

Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

Chart 9

Trust in Pharmaceutical Companies

How much do you trust pharmaceutical companies to…



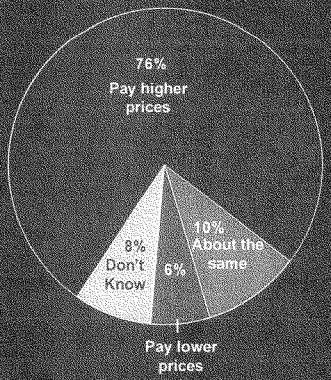
Note: "Don't know" responses not shown

Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2006)

Chart 10

Rx Drug Cost in the U.S. Relative to Other Countries

In general, do you think people in this country pay higher or lower prices than people in Canada, Mexico, and Western Europe pay for the same prescription drug, or do you think they pay about the same amount?



Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2006)

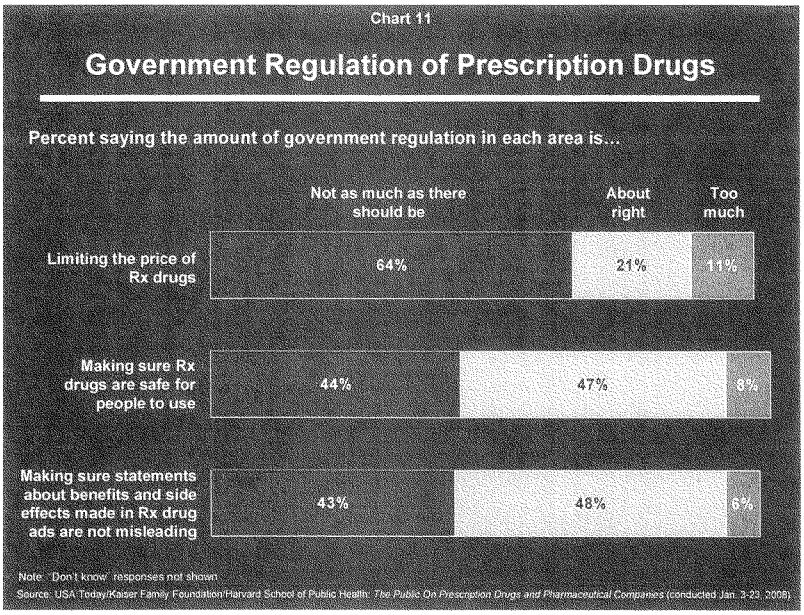


Chart 11
Government Regulation of Prescription Drugs
Percent saying the amount of government regulation in each area is...
Not as much as there should be
About right
Too much
Limiting the price of Rx drugs
64%
21%
11%
Making sure Rx drugs are safe for people to use
44%
47%
8%
Making sure statements about benefits and side effects made in Rx drug ads are not misleading
43%
48%
6%
Note: "Don't know" responses not shown
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2006)

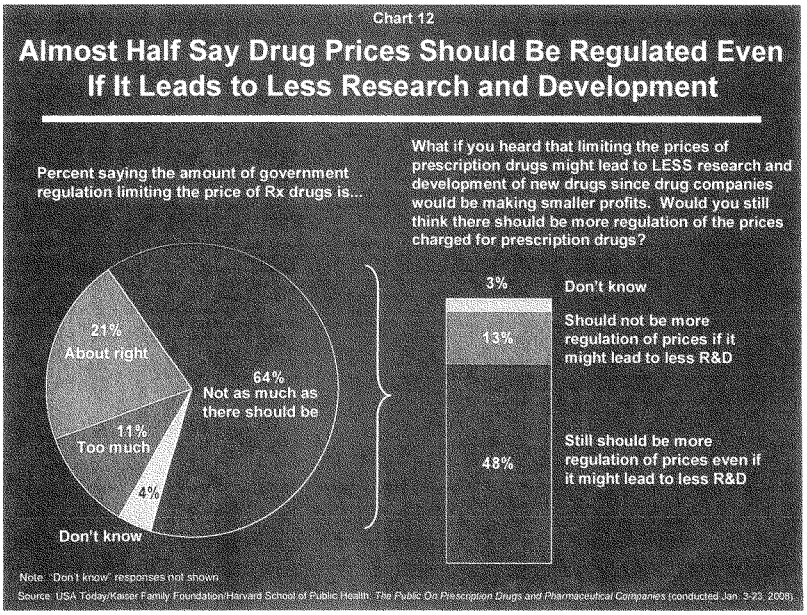


Chart 12
Almost Half Say Drug Prices Should Be Regulated Even If It Leads to Less Research and Development
Percent saying the amount of government regulation limiting the price of Rx drugs is...
21%
About right
64%
Not as much as there should be
11%
Too much
4%
Don't know
What if you heard that limiting the prices of prescription drugs might lead to LESS research and development of new drugs since drug companies would be making smaller profits. Would you still think there should be more regulation of the prices charged for prescription drugs?
3%
Don't know
13%
Should not be more regulation of prices if it might lead to less R&D
48%
Still should be more regulation of prices even if it might lead to less R&D
Note: "Don't know" responses not shown
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2006)

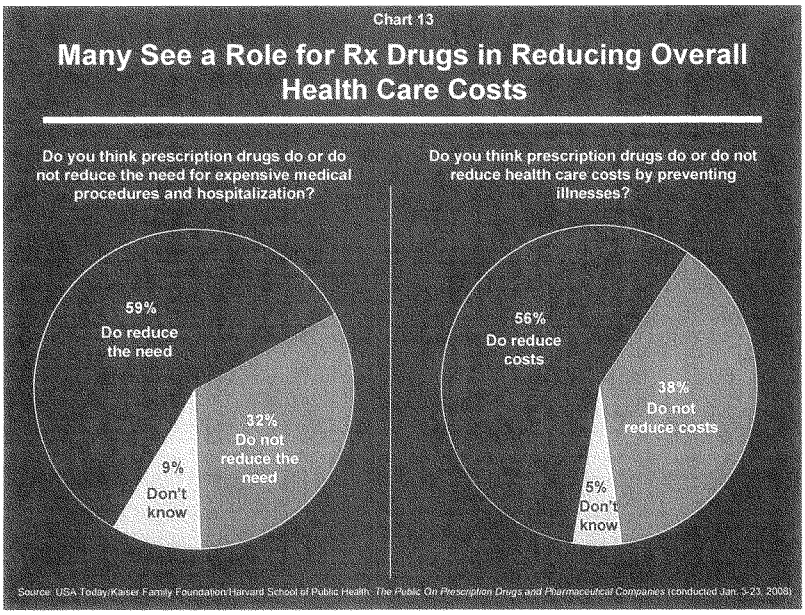


Chart 13
Many See a Role for Rx Drugs in Reducing Overall Health Care Costs
Do you think prescription drugs do or do not reduce the need for expensive medical procedures and hospitalization?
59% Do reduce the need
32% Do not reduce the need
9% Don't know
Do you think prescription drugs do or do not reduce health care costs by preventing illnesses?
56% Do reduce costs
38% Do not reduce costs
5% Don't know
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2006)

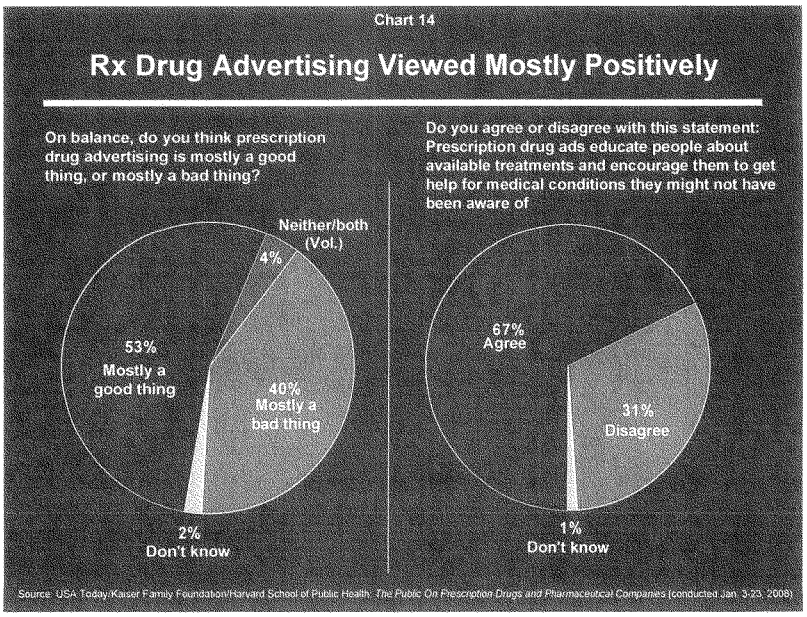


Chart 14
Rx Drug Advertising Viewed Mostly Positively
On balance, do you think prescription drug advertising is mostly a good thing, or mostly a bad thing?
Neither/both (Vol.) 4%
53% Mostly a good thing
40% Mostly a bad thing
2% Don't know
Do you agree or disagree with this statement: Prescription drug ads educate people about available treatments and encourage them to get help for medical conditions they might not have been aware of
67% Agree
31% Disagree
1% Don't know
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2006)

Chart 15

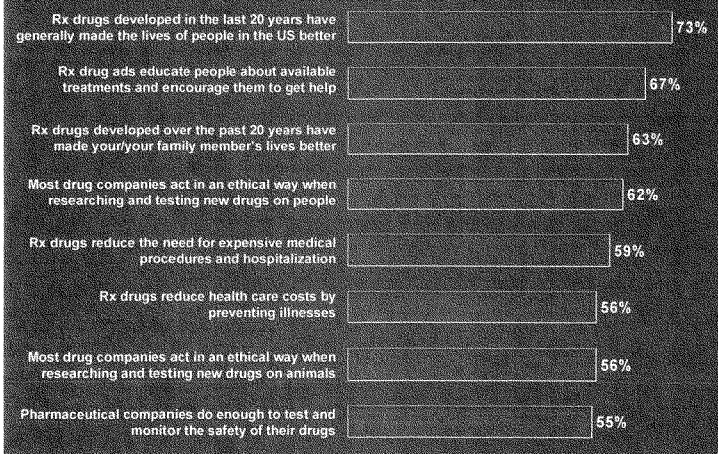
Some Negative Views of Rx Drug Ads

Negatives of prescription drug ads	% who agree with each statement	% who say each bothers them "a lot"
The cost of ads makes Rx drugs too expensive	77%	41%
Ads for Rx drugs encourage people to take medicine they don't need	66%	34%
There are too many Rx drug ads on television	68%	27%
Many Rx drug ads are too sexually explicit	46%	20%

Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

Chart 16

Summary: Top Positive Views of Rx Drugs and Drug Companies



Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

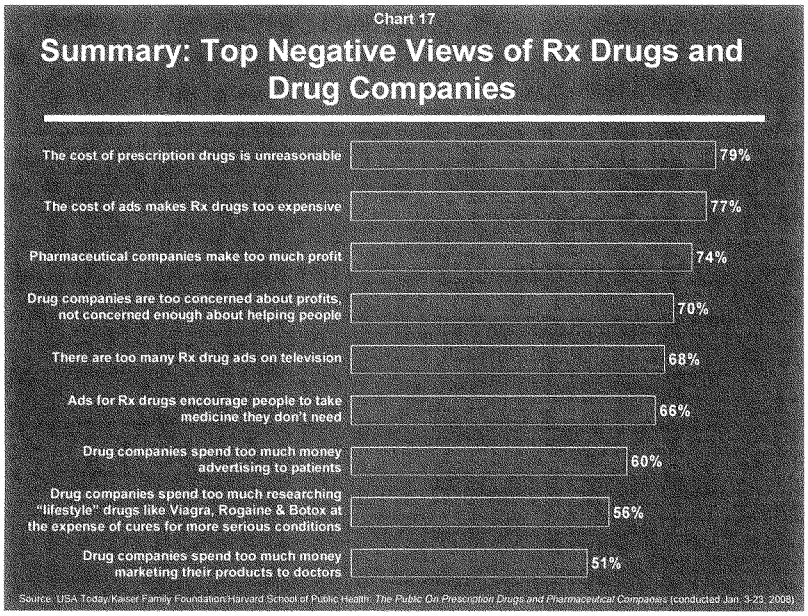


Chart 17
Summary: Top Negative Views of Rx Drugs and Drug Companies
The cost of prescription drugs is unreasonable
79%
The cost of ads makes Rx drugs too expensive
77%
Pharmaceutical companies make too much profit
74%
Drug companies are too concerned about profits, not concerned enough about helping people
70%
There are too many Rx drug ads on television
68%
Ads for Rx drugs encourage people to take medicine they don't need
66%
Drug companies spend too much money advertising to patients
60%
Drug companies spend too much researching "lifestyle" drugs like Viagra, Rogaine & Botox at the expense of cures for more serious conditions
56%
Drug companies spend too much money marketing their products to doctors
51%
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

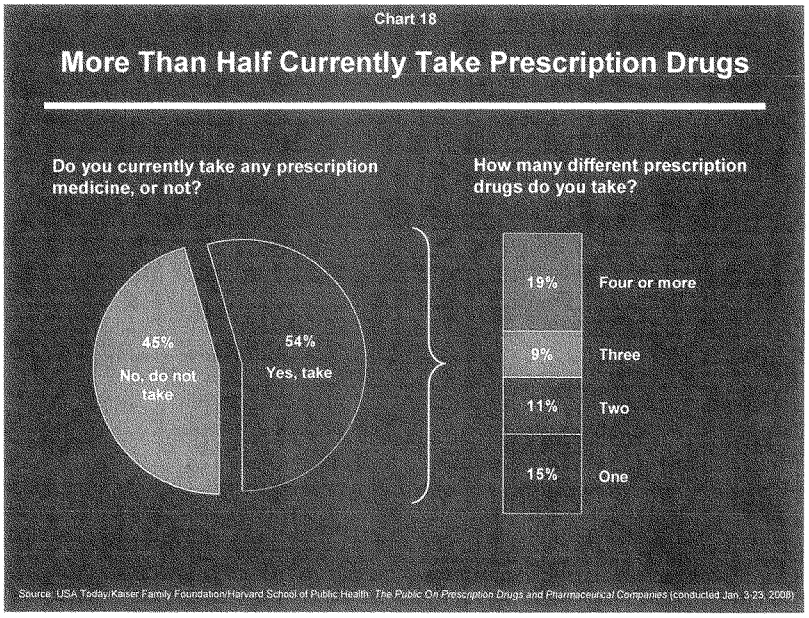
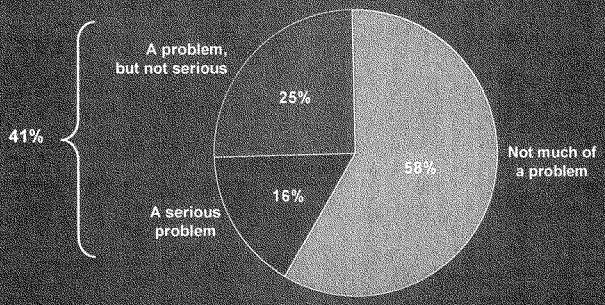


Chart 18
More Than Half Currently Take Prescription Drugs
Do you currently take any prescription medicine, or not?
How many different prescription drugs do you take?
45%
No, do not take
54%
Yes, take
19%
Four or more
9%
Three
11%
Two
15%
One
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

Chart 19

Significant Minority Has Problems Paying for Rx Drugs

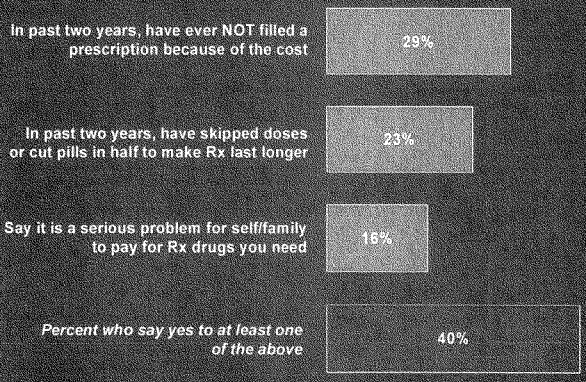
How much of a problem is it for you or your family to pay for prescription medicines that you need?



Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

Chart 20

Serious Problems Paying, Not Filling Prescriptions and Skipping Rx Doses Because of Cost



Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

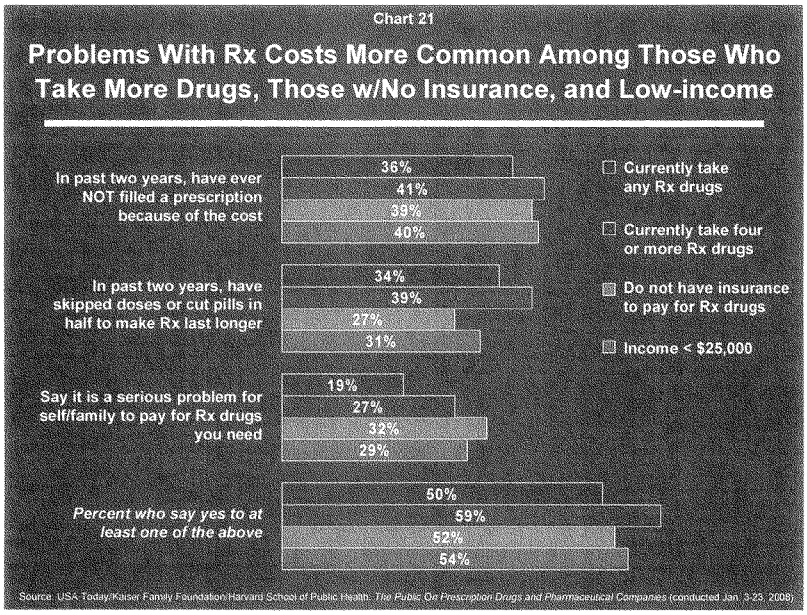


Chart 21
Problems With Rx Costs More Common Among Those Who Take More Drugs, Those w/No Insurance, and Low-income
In past two years, have ever NOT filled a prescription because of the cost
36%
41%
38%
40%
In past two years, have skipped doses or cut pills in half to make Rx last longer
34%
39%
27%
31%
Say it is a serious problem for self/family to pay for Rx drugs you need
19%
27%
32%
29%
Percent who say yes to at least one of the above
50%
59%
52%
54%
Currently take any Rx drugs
Currently take four or more Rx drugs
Do not have insurance to pay for Rx drugs
Income < $25,000
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

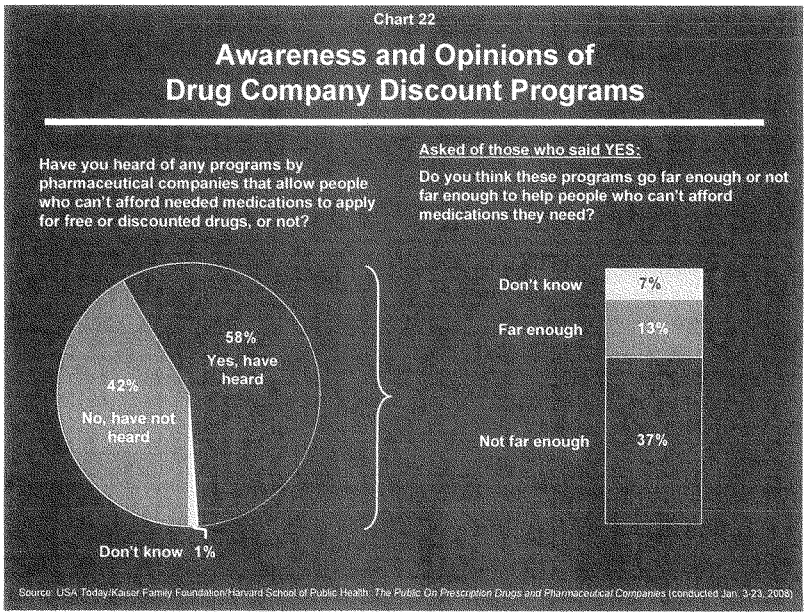


Chart 22
Awareness and Opinions of Drug Company Discount Programs
Have you heard of any programs by pharmaceutical companies that allow people who can't afford needed medications to apply for free or discounted drugs, or not?
58%
Yes, have heard
42%
No, have not heard
Don't know 1%
Asked of those who said YES:
Do you think these programs go far enough or not far enough to help people who can't afford medications they need?
Don't know 7%
Far enough 13%
Not far enough 37%
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

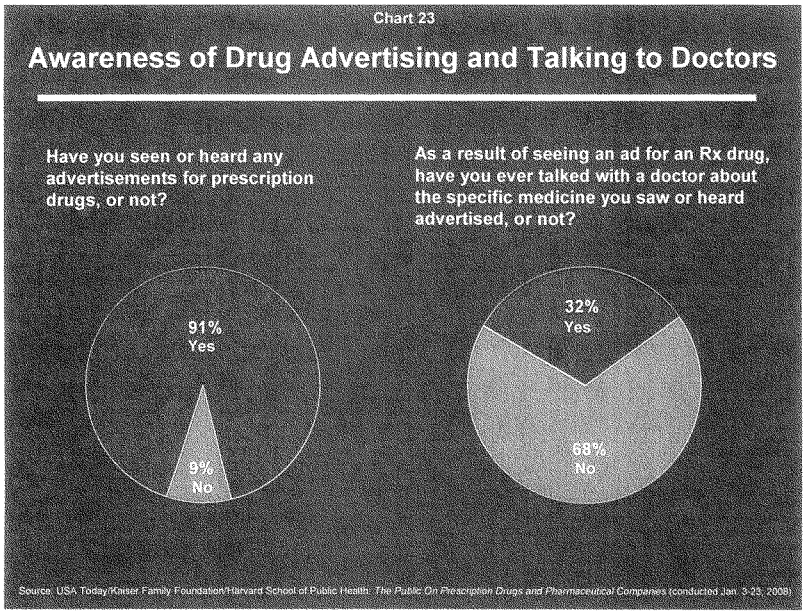


Chart 23
Awareness of Drug Advertising and Talking to Doctors
Have you seen or heard any advertisements for prescription drugs, or not?
91% Yes
9% No
As a result of seeing an ad for an Rx drug, have you ever talked with a doctor about the specific medicine you saw or heard advertised, or not?
32% Yes
68% No
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

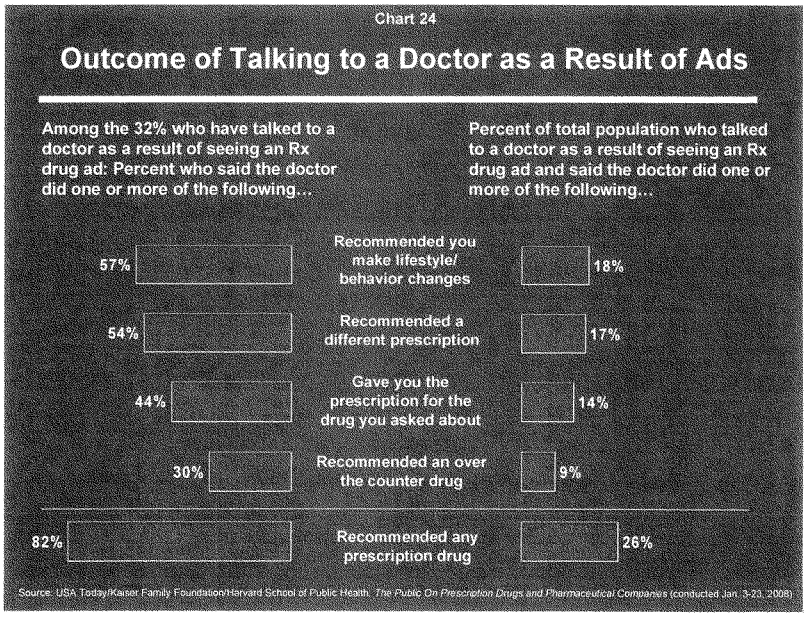
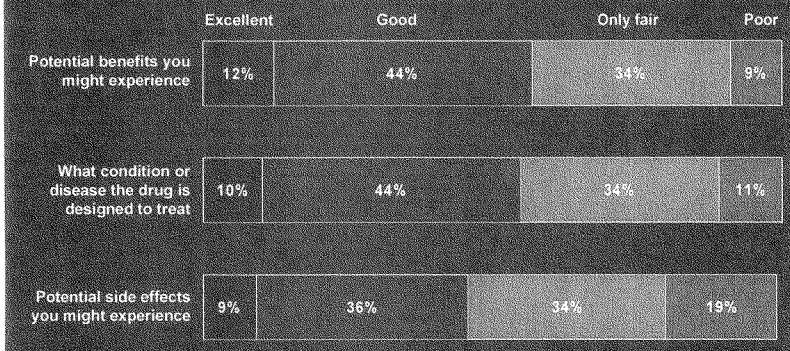


Chart 24
Outcome of Talking to a Doctor as a Result of Ads
Among the 32% who have talked to a doctor as a result of seeing an Rx drug ad: Percent who said the doctor did one or more of the following…
Percent of total population who talked to a doctor as a result of seeing an Rx drug ad and said the doctor did one or more of the following…
57% Recommended you make lifestyle/ behavior changes 18%
54% Recommended a different prescription 17%
44% Gave you the prescription for the drug you asked about 14%
30% Recommended an over the counter drug 9%
82% Recommended any prescription drug 26%
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

Chart 25

Are Drug Ads Doing a Good Job Informing the Public?

Do prescription drug advertisements do an excellent job, a good job, only a fair job, or a poor job telling you about the following... ?

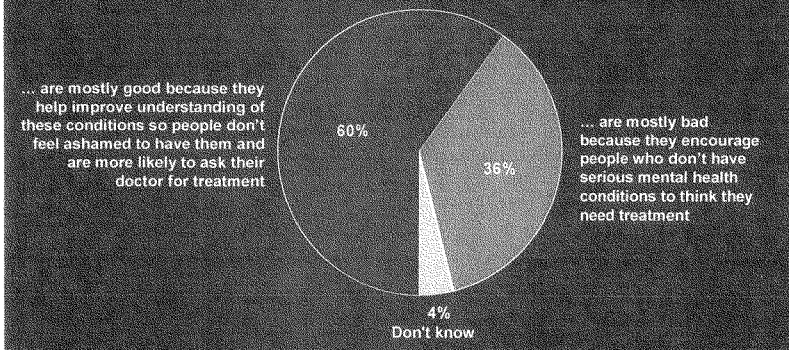


Note: "Don't know" responses not shown
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

Chart 26

Perception of Drug Ads for Mental Health Conditions

Which comes closer to your view:
Advertisements for prescription drugs to treat mental health conditions like depression and anxiety...?



Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2008)

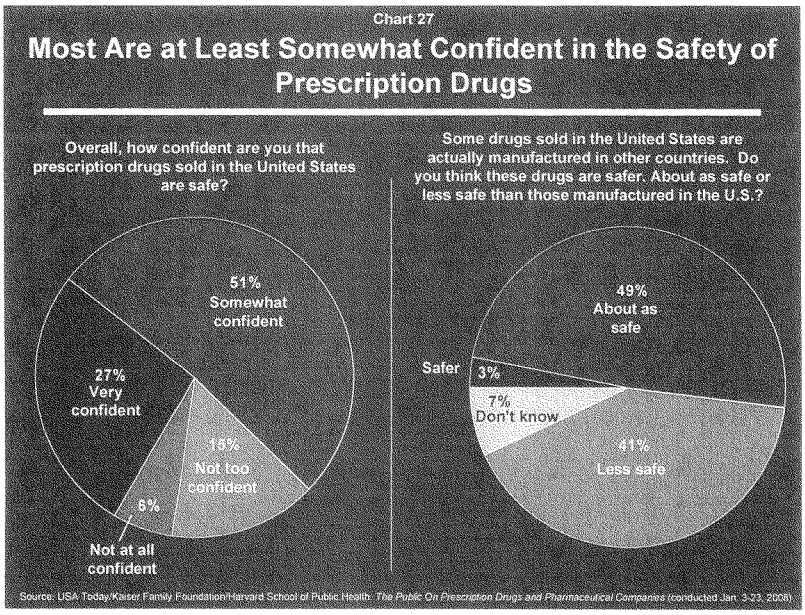


Chart 27
Most Are at Least Somewhat Confident in the Safety of Prescription Drugs
Overall, how confident are you that prescription drugs sold in the United States are safe?
51% Somewhat confident
27% Very confident
15% Not too confident
6% Not at all confident
Some drugs sold in the United States are actually manufactured in other countries. Do you think these drugs are safer, about as safe or less safe than those manufactured in the U.S.?
49% About as safe
Safer 3%
7% Don't know
41% Less safe
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)


Chart 28
Pharmaceutical Companies' Safety Testing for Prescription Drugs
Do you think pharmaceutical companies do enough to test and monitor the safety of their drugs, or not?
55% Yes, do enough
41% No, do not do enough
4% Don't know
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2008)

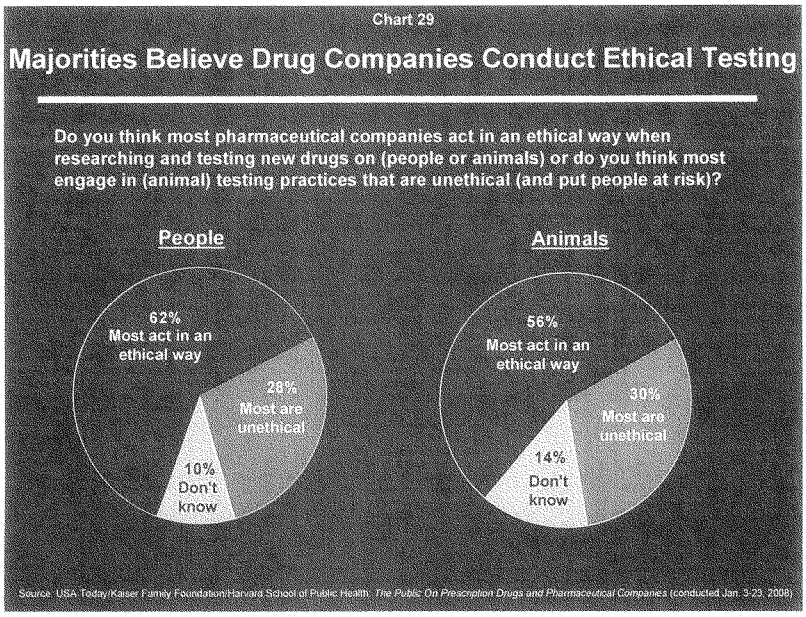


Chart 29
Majorities Believe Drug Companies Conduct Ethical Testing
Do you think most pharmaceutical companies act in an ethical way when researching and testing new drugs on (people or animals) or do you think most engage in (animal) testing practices that are unethical (and put people at risk)?
People
62% Most act in an ethical way
28% Most are unethical
10% Don't know
Animals
56% Most act in an ethical way
30% Most are unethical
14% Don't know
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2006)

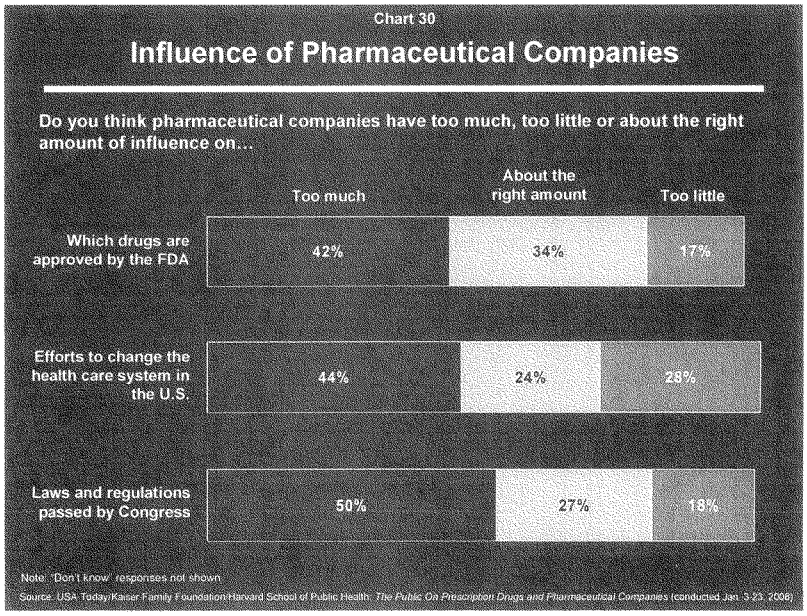
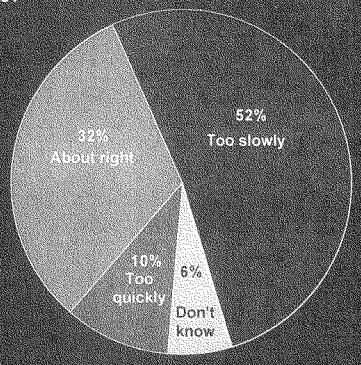


Chart 30
Influence of Pharmaceutical Companies
Do you think pharmaceutical companies have too much, too little or about the right amount of influence on...
Too much
About the right amount
Too little
Which drugs are approved by the FDA
42%
34%
17%
Efforts to change the health care system in the U.S.
44%
24%
28%
Laws and regulations passed by Congress
50%
27%
18%
Note: "Don't know" responses not shown
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2006)

Chart 31

Views of Governmental Review and Approval For Prescription Drugs

In general, do you think the government moves too quickly or too slowly to review and approve new prescription drugs, or do you think they take about the right amount of time?

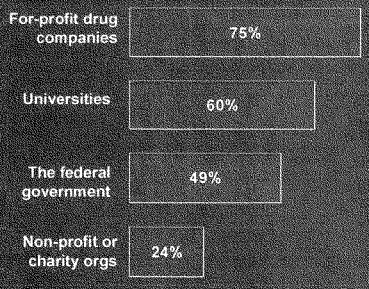


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2006)

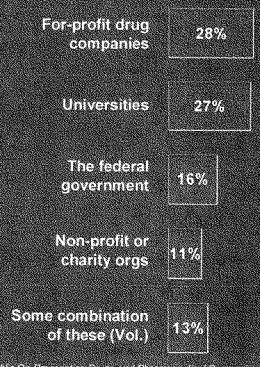
Chart 32

Role of Drug Companies and Other Groups in Drug Research and Development

How big a role do you think the following play in researching and developing new drugs? (percent saying each plays a "major role")



Who do you think SHOULD be primarily responsible for developing new drugs? (percent choosing each when forced to choose)

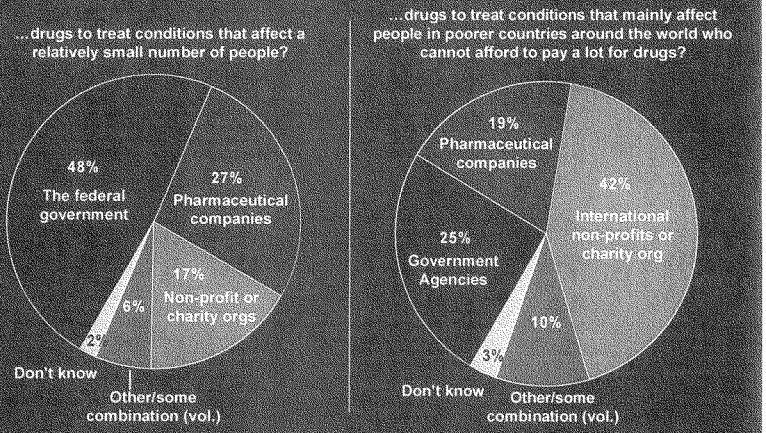


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health: *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2006)

Chart 33

Responsibility for Research on Orphan Drugs and Drugs for People in Poor Countries

Who should be responsible for making sure research is conducted on…

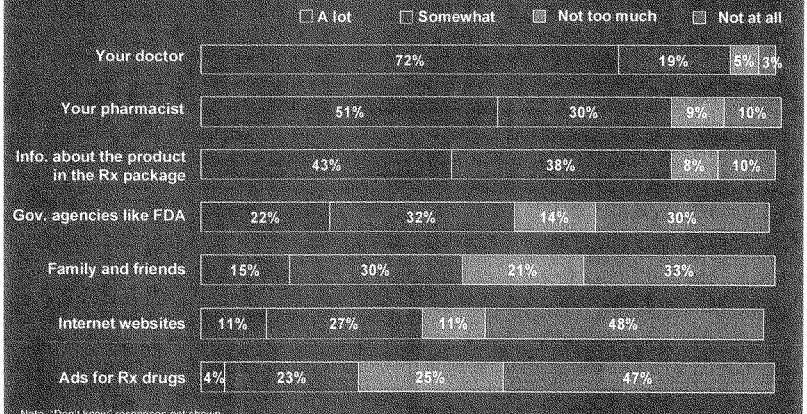


Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health. *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2006)

Chart 34

Sources of Information for Rx Drugs

Please tell me how much you rely on each of the following sources to provide accurate information about prescription medicines:



Note: "Don't know" responses not shown

Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health. *The Public On Prescription Drugs and Pharmaceutical Companies* (conducted Jan. 3-23, 2006)

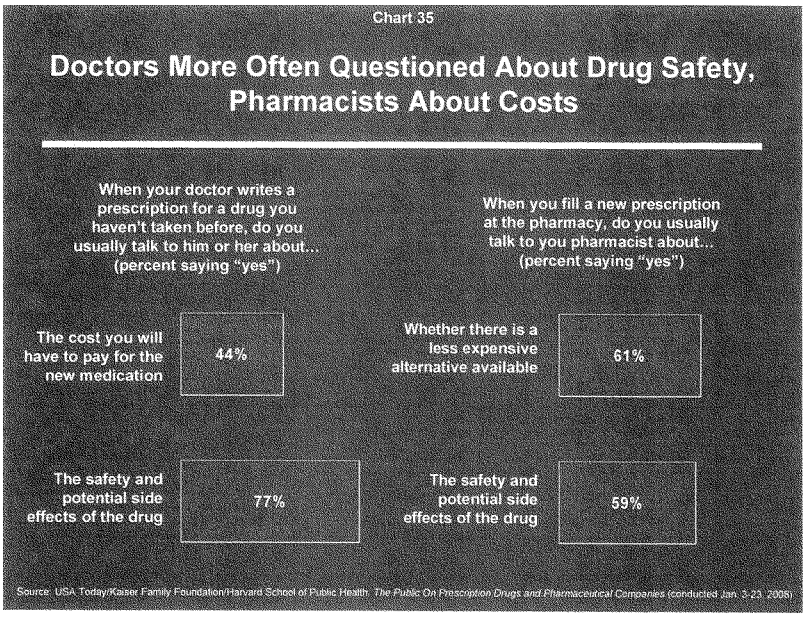


Chart 35
Doctors More Often Questioned About Drug Safety, Pharmacists About Costs
When your doctor writes a prescription for a drug you haven't taken before, do you usually talk to him or her about... (percent saying "yes")
The cost you will have to pay for the new medication
44%
The safety and potential side effects of the drug
77%
When you fill a new prescription at the pharmacy, do you usually talk to you pharmacist about... (percent saying "yes")
Whether there is a less expensive alternative available
61%
The safety and potential side effects of the drug
59%
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2006)

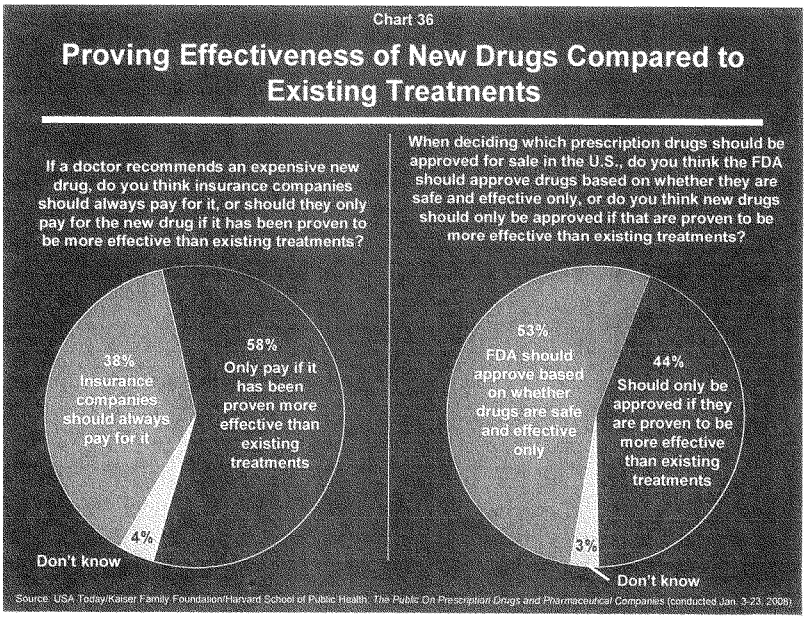


Chart 36
Proving Effectiveness of New Drugs Compared to Existing Treatments
If a doctor recommends an expensive new drug, do you think insurance companies should always pay for it, or should they only pay for the new drug if it has been proven to be more effective than existing treatments?
38%
Insurance companies should always pay for it
58%
Only pay if it has been proven more effective than existing treatments
4%
Don't know
When deciding which prescription drugs should be approved for sale in the U.S., do you think the FDA should approve drugs based on whether they are safe and effective only, or do you think new drugs should only be approved if that are proven to be more effective than existing treatments?
53%
FDA should approve based on whether drugs are safe and effective only
44%
Should only be approved if they are proven to be more effective than existing treatments
3%
Don't know
Source: USA Today/Kaiser Family Foundation/Harvard School of Public Health, The Public On Prescription Drugs and Pharmaceutical Companies (conducted Jan. 3-23, 2006)



HARVARD
School of Public Health

The Henry J. Kaiser Family Foundation

Headquarters
2400 Sand Hill Road
Menlo Park, CA 94025
Phone: (650) 854-9400 Fax: (650) 854-4800

Washington Offices and
Barbara Jordan Conference Center
1330 G Street, NW
Washington, DC 20005
Phone: (202) 347-5270 Fax: (202) 347-5274

www.kff.org

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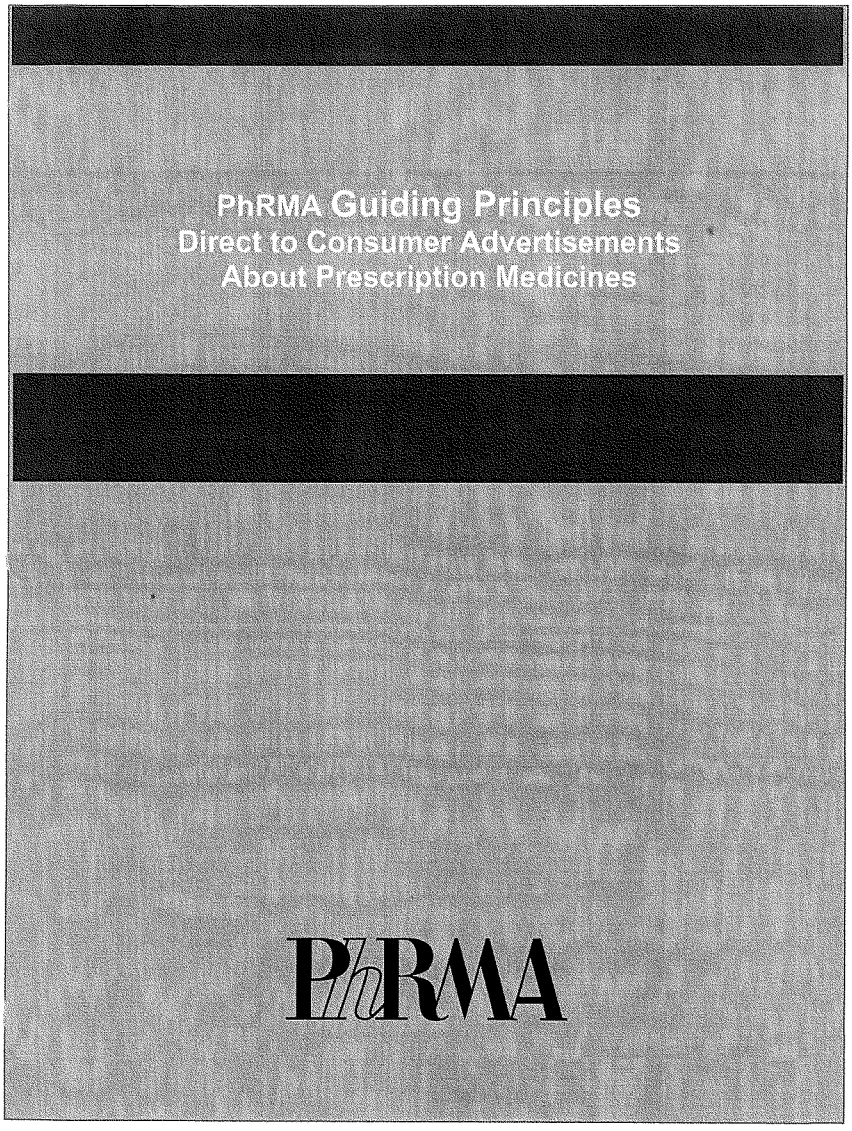
The Kaiser Family Foundation is a non-profit, private operating foundation dedicated to providing information and analysis on health care issues to policymakers, the media, the health care community and the general public. The Foundation is not associated with Kaiser Permanente or Kaiser Industries.

Harvard School of Public Health is dedicated to advancing the public's health through learning, discovery, and communication. More than 300 faculty members are engaged in teaching and training the 800-plus student body in a broad spectrum of disciplines crucial to the health and well being of individuals and populations around the world. Programs and projects range from the molecular biology of AIDS vaccines to the epidemiology of cancer; from risk analysis to violence prevention; from maternal and children's health to quality of care measurement; from health care management to international health and human rights.


PhRMA Guiding Principles
Direct to Consumer Advertisements
About Prescription Medicines
PhRMA

PhRMA Guiding Principles
Direct to Consumer Advertisements
About Prescription Medicines

Preamble

Given the progress that continues to be made in society's battle against disease, patients are seeking more information about medical problems and potential treatments so they can better understand their health care options and communicate effectively with their physicians. An important benefit of direct-to-consumer (DTC) advertising is that it fosters an informed conversation about health, disease and treatments between patients and their health care practitioners.

A strong empirical record demonstrates that DTC communications about prescription medicines serve the public health by:

- Increasing awareness about diseases;
- Educating patients about treatment options;
- Motivating patients to contact their physicians and engage in a dialogue about health concerns;
- Increasing the likelihood that patients will receive appropriate care for conditions that are frequently under-diagnosed and under-treated; and
- Encouraging compliance with prescription drug treatment regimens.

The Pharmaceutical Research and Manufacturers of America (PhRMA), represents America's leading pharmaceutical research and biotechnology companies. As the companies responsible for developing new and innovative medicines, PhRMA members want patients and consumers to talk to their physicians about the medicines that may help them and to fully understand the known risks regarding these medicines. We know that DTC communications, particularly DTC television advertising, can be a powerful tool for reaching and educating millions of people, and we are committed to ensuring that our DTC communications provide accurate, accessible and useful health information to patients and consumers. DTC advertising of such important and powerful products as prescription drugs should be responsibly designed to achieve these goals and to encourage the appropriate use of these products.

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First and foremost, we have a responsibility to ensure that our DTC communications comply with the regulations of the Food & Drug Administration (FDA). In general, the FDA requires all DTC information:

- To be accurate and not misleading;
- To make claims only when supported by substantial evidence;
- To reflect balance between risks and benefits; and
- To be consistent with the FDA-approved labeling.

The innovative pharmaceutical industry takes its responsibilities to comply with FDA requirements seriously. Companies devote substantial time and effort, and often ask for input from FDA, to ensure that DTC communications are accurate, fairly balanced and meet all applicable legal requirements. PhRMA member companies will engage in a dialogue with FDA to maximize opportunities for FDA review of DTC advertising prior to release, consistent with these principles and the agency's priorities and resources.

Beyond meeting their legal obligations, companies strive to deliver messages that fundamentally serve to educate patients and consumers and encourage them to seek guidance from their health care professionals.

To express the commitment of PhRMA members to deliver DTC communications that serve as valuable contributors to public health, PhRMA has established the following voluntary guiding principles.

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Guiding Principles

1. These Principles are premised on the recognition that DTC advertising of prescription medicines can benefit the public health by increasing awareness about diseases, educating patients about treatment options, motivating patients to contact their physicians and engage in a dialogue about health concerns, increasing the likelihood that patients will receive appropriate care for conditions that are frequently under-diagnosed and under-treated, and encouraging compliance with prescription drug treatment regimens.

2. In accordance with FDA regulations, all DTC information should be accurate and not misleading, should make claims only when supported by substantial evidence, should reflect balance between risks and benefits, and should be consistent with FDA approved labeling.

3. DTC television and print advertising which is designed to market a prescription drug should also be designed to responsibly educate the consumer about that medicine and, where appropriate, the condition for which it may be prescribed.

4. DTC television and print advertising of prescription drugs should clearly indicate that the medicine is a prescription drug to distinguish such advertising from other advertising for non-prescription products.

5. DTC television and print advertising should foster responsible communications between patients and health care professionals to help patients achieve better health and a more complete appreciation of both the health benefits and the known risks associated with the medicine being advertised.

6. In order to foster responsible communication between patients and health care professionals, companies should spend an appropriate amount of time to educate health professionals about a new medicine or a new therapeutic indication before commencing the first DTC advertising campaign. In determining what constitutes an appropriate time, companies should take into account the relative importance of informing patients of the availability of a new medicine, the complexity of the risk-benefit profile of that new medicine and health care professionals' knowledge of the condition being treated. Companies should continue to educate health care professionals as additional valid information about a new medicine is obtained from all reliable sources.

7. Working with the FDA, companies should continue to responsibly alter or discontinue a DTC advertising campaign should new and reliable information indicate a serious previously unknown safety risk.

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8. Companies should submit all new DTC television advertisements to the FDA before releasing these advertisements for broadcast.

9. DTC television and print advertising should include information about the availability of other options such as diet and lifestyle changes where appropriate for the advertised condition.

10. DTC television advertising that identifies a product by name should clearly state the health conditions for which the medicine is approved and the major risks associated with the medicine being advertised.

11. DTC television and print advertising should be designed to achieve a balanced presentation of both the benefits and the risks associated with the advertised prescription medicine. Specifically, risks and safety information in DTC television advertising should be presented in clear, understandable language, without distraction from the content, and in a manner that supports the responsible dialogue between patients and health care professionals.

12. All DTC advertising should respect the seriousness of the health conditions and the medicine being advertised.

13. In terms of content and placement, DTC television and print advertisements should be targeted to avoid audiences that are not age appropriate for the messages involved.

14. Companies are encouraged to promote health and disease awareness as part of their DTC advertising.

15. Companies are encouraged to include information in all DTC advertising, where feasible, about help for the uninsured and underinsured.

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Accountability for the Guiding Principles

Companies commit to establishing internal processes to ensure compliance with these guiding principles. Companies also commit to distributing these guidelines internally and to their advertising agencies.

Each company's intentions with regard to these guiding principles will be made public.

PhRMA will establish an office of accountability that will be responsible for receiving comments from the general public and from health care professionals regarding DTC advertising conducted by any signatory company to these principles. Any company that publicly states that it will follow the principles will be considered a signatory company.

The PhRMA office of accountability will provide to the signatory company at issue any comment that is reasonably related to compliance with the principles.

The PhRMA office of accountability will issue periodic reports to the public regarding the nature of the comments and the signatory companies' responses, and will provide a copy of each report to the FDA.

One year after the effective date of the Principles, the PhRMA office of accountability will select an independent panel of credible individuals to review reports of that year, to track the overall trends in the industry as they relate to the Principles, and to make recommendations in accordance with the Principles. The panel's report will be included in the next report of the PhRMA office of accountability.

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PhRMA Guiding Principles
Direct to Consumer Advertisements
About Prescription Medicines

Questions and Answers

Q: *What is meant by a "direct to consumer television advertisement" in the context of these principles?*

A: A direct to consumer television advertisement is a portion of television air time on broadcast or cable television that is bought by a company for the purpose of presenting information about one or more of the company's medicines. A DTC television advertisement does not include sponsorship of activities.

Q: *What is meant by "direct to consumer print advertisement" in the context of these principles?*

A: A direct to consumer print advertisement is space that is bought by a company in newspaper or magazine publications targeted to patients or consumers, or a direct mail communication paid for and disseminated by a company to patients or consumers, for the purpose of presenting information about one or more of the company's medicines. A DTC print advertisement does not include sponsorship of activities.

Q: *How long must a company wait under Principle 6 before advertising a new medicine after the medicine is approved by FDA?*

A: Principle 6 demonstrates the companies' commitment to devote sufficient resources and time to health care professional education before launching a direct to consumer advertising campaign. Principle 6 ensures that health care professionals will have a reasonable opportunity to learn about new medications before their patients ask questions about them so they will have accurate, up-to-date information to use in responding to patients' inquiries and guiding patients to the most appropriate treatment option. Establishing a single uniform waiting period for all companies and all medicines could have the unintended consequence of denying patients important information about new medicines, even after health care professionals have been well educated. Each company will decide for itself how best to implement an effective educational program, taking into account such factors as health care professionals' knowledge of the condition being treated, the severity and/or prevalence of the condition, the novelty of the new treatment, and the complexity of the medicine's risk-benefit profile and directions for use.

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Q: *Does Principle 8 require companies to do more than what is already required under current FDA regulations?*

A: Yes. Current law provides that companies must submit their DTC television advertisements to FDA upon first use for FDA's review at its discretion. Under Principle 8, while not intending to place additional burdens on FDA, companies commit to submitting new DTC television advertisements to FDA earlier than currently required and a reasonable time in advance of first use to give FDA the opportunity to comment, consistent with its priorities and resources. Companies also commit to inform FDA when they submit an advertisement of the earliest date the advertisement is scheduled to air.

Q: *Should companies notify FDA if they are specifically requesting feedback on a particular advertisement submitted under Principle 8?*

A: In order to permit FDA to allocate its resources effectively, companies should notify FDA if they are specifically requesting feedback on a submitted DTC advertisement. Companies also should indicate whether the requested FDA review is time-sensitive to help FDA prioritize its review activities. As a general matter, we understand that FDA expects companies to submit the following information with the submitted DTC advertisement: (1) a statement indicating whether the company is submitting the advertisement for prior Agency review and feedback, or for the Agency's information; and (2) if feedback is requested, a statement identifying whether the company is requesting FDA review on a priority basis; (3) a brief description of the reasons for any request for priority review (e.g., identifying the basis for the submission and the nature of any change the company deems significant) and (4) the earliest date the company plans to finalize the advertisement. Companies typically should reserve a priority review request for those submissions that are most time-sensitive, keeping in mind that FDA may choose to review only one iteration of a particular new DTC advertisement on a priority basis.

Q: *PhRMA states that, under Principle 8, companies should submit new DTC television advertisements to the FDA a reasonable time before releasing the advertisement for broadcast to give FDA the opportunity to comment, consistent with its priorities and resources. What constitutes "a reasonable time" in this context?*

A: The precise time frame for submission of a particular DTC advertisement will vary depending on the advertisement in question and purpose of the submission. If a company is specifically requesting feedback from FDA, either by priority review or standard review, it should submit the DTC advertisement far enough in advance to permit the Agency to perform the requested review. Although the timing of FDA's review of DTC advertisements will be dictated by the Agency's priorities and resources, a company seeking priority review will maximize its opportunity to receive

comments from the Agency if the company allows 30 calendar days for FDA review and comment. A company seeking non-priority review for a particular advertisement should try to allow more than 30 calendar days for FDA review, while less lead time could be appropriate if a company is submitting a particular advertisement for the Agency's information.

Q: *Does Principle 8 require companies to submit a new DTC television advertisement to FDA in advance, even if the advertisement reflects only minor changes to a previously submitted advertisement?*

A: No. Under Principle 8, companies should submit only new television advertisements or advertisements that have been changed in a way that the companies believe is significant. For instance, where a company changes an existing advertisement—possibly by changing a telephone number listed on the screen or by replacing an actor—to use for a different targeted audience, but does not substantially change the advertisement's script or theme, then the company is not required under Principle 8 to submit the changed advertisement to FDA. However, where a company changes an advertisement so that the benefit and/or risk information is presented in a different way, the company likely has made a significant change, and the advertisement should be submitted to FDA. Other circumstances that typically would trigger submission of DTC television advertisements under Principle 8 include (1) introduction of a new or never-before-advertised product; (2) new indications for existing products; (3) significant new risk information; (4) new comparative claims or patient outcome claims; or (5) new patient populations.

Q: *Does Principle 8 necessarily require a company to submit the final version of a new DTC television advertisement to FDA prior to releasing the advertisement for broadcast?*

A: No. The details of what will be submitted may be addressed in dialogue between companies and FDA.

Q: *Would additional dialogue between companies and the FDA be helpful as Principle 8 is implemented?*

A: Yes. Additional dialogue should occur to maximize opportunities for FDA review of DTC television advertising prior to release, consistent with this principle and the agency's priorities and resources.

Q: *Under Principles 3 and 9, does a company have to mention another medication that may also be appropriate for treating the advertised condition?*

A: No. These principles are intended to encourage companies to include in their advertisements information about therapeutic options and appropriate steps patients could take (which may or may not include other medicines), in consultation with health care professionals, to treat their disease or condition. This is consistent with the pharmaceutical industry's goal of helping patients achieve better overall health.

Q: *Is there only one right way to present risk information in advertisements?*

A: No. An advertisement will comply with Principle 11 if it presents information about the medicine's risks in a way that patients are reasonably likely to take in and understand this information. For television advertisements, the visual and audio presentation of risk information should be similar in terms of prominence and clarity to the visual and audio presentation of other information about the medicine. Of course, even the most informative advertisements can't provide information on all possible risks that may relate to each individual patient. Therefore, the conversation between a patient and a health care professional is critical to the patient's understanding of whether a medicine is right for that individual patient. DTC advertisements should motivate patients to ask their health care professionals for more information about a medicine's risks and benefits. These objectives can be achieved in a variety of ways, and each company will exercise its judgment consistent with FDA requirements.

Q: *What happens if a comment from the public about a company's DTC advertisement conflicts with recommendations or comments the company has received from FDA regarding the advertisement?*

A: The FDA has the authority to determine whether a particular advertisement is consistent with FDA regulations. If FDA chooses to give recommendations or comments on a particular DTC advertisement and the company follows those recommendations or comments, the company will be able to respond to any complaint regarding that aspect of the DTC advertisement that it complies with the PhRMA Principles by virtue of the fact that it followed FDA's recommendations.

PhRMA

Q: *Does Principle 12 suggest that all advertisements should be somber in tone and should not employ lightness, humor or entertainment?*

A: No. Principle 12 recognizes that health conditions and medical treatments are serious issues for patients. While humor or entertainment may not be appropriate in conveying all messages, they may be effective tools for attracting public attention to a particular disease or treatment, reducing any stigma associated with the condition, communicating educational messages about health conditions, and motivating patients to discuss those conditions openly with their health care providers.

Q: *What criteria should be applied to determine whether a company has complied with Principle 13 and targeted its advertising to avoid audiences that are not age appropriate for the messages in the advertisements?*

A: Advertisements containing content that may be inappropriate for children should be targeted to programs or publications that are reasonably expected to draw an audience of approximately 80 percent adults (18 years or older). Companies will be individually responsible for examining reliable, up-to-date audience composition data, to the extent that information is available, to determine whether a particular program or publication is reasonably likely to attract an audience that is age appropriate for a particular advertisement.

Revised November 2005

PhRMA

INSTITUTE OF MEDICINE

EPORT BRIEF • SEPTEMBER 2006

THE FUTURE OF DRUG SAFETY: ACTION STEPS FOR CONGRESS



The Institute of Medicine's Committee on the Assessment of the U.S. Drug Safety System intends that the 25 recommendations in its report will bring the strengths of the preapproval process (data, regulatory authority, organizational function and capabilities, and resources) to the postapproval phase in order to fulfill a lifecycle approach to the study, regulation, and communication about the risks and benefits of drugs.

CLARIFY FDA'S REGULATORY AUTHORITY

The Food and Drug Administration's authorities must be clarified and strengthened to empower the agency to take rapid and decisive actions when necessary and appropriate. FDA lacks the clear, unambiguous authority needed to enforce sponsor compliance with regulatory requirements and instead relies on the prospect of productive negotiations with industry.

5.1 The committee recommends that Congress ensure that FDA has the ability to require such postmarketing risk assessment and risk management programs as are needed to monitor and ensure safe use of drug products. These conditions may be imposed both before and after approval of a new drug, new indication, or new dosage, as well as after identification of new contraindications or patterns of adverse events. The limitations imposed should match the specific safety concerns and benefits presented by the drug product. The risk assessment and risk management program may include:

a) Distribution conditioned on compliance with agency-initiated changes in drug labels.
b) Distribution conditioned on specific warnings to be incorporated into all promotional materials (including broadcast DTC advertising).
c) Distribution conditioned on a moratorium on direct to consumer advertising.
d) Distribution restricted to certain facilities, pharmacists, or physicians with special training or experience.
e) Distribution conditioned on the performance of specified medical procedures.
f) Distribution conditioned on the performance of specified additional clinical trials or other studies.
g) Distribution conditioned on the maintenance of an active adverse event surveillance system.

5.2 The committee recommends that Congress provide oversight and enact any needed legislation to ensure compliance by both FDA and drug sponsors with the provisions listed above. FDA needs increased enforcement authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.

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REQUIRE SYMBOL TO ALERT CONSUMERS TO NEW PRODUCTS AND DENOTE HEIGHTENED REGULATORY ATTENTION

Marking the label and all promotional material for newly approved drugs or indications with a special symbol will help increase awareness of the nature of newly approved therapies (for example, the incompleteness of information on safety).

5.3 The committee recommends that Congress amend the Federal Food, Drug and Cosmetic Act to require that product labels carry a special symbol such as the black triangle used in the UK or an equivalent symbol for new drugs, new combinations of active substances, and new systems of delivery of existing drugs. FDA should restrict direct-to-consumer advertising during the period of time the special symbol is in effect. The symbol should remain on the drug label and related materials for 2 years unless FDA chooses to shorten or extend the period on a case by case basis.

ESTABLISH PERFORMANCE GOALS FOR SAFETY

The Prescription Drug User Fee Act mechanism that accounts for over half of the Center for Drug Evaluation and Research's funding and the reporting requirements associated with the user-fee program are excessively oriented toward supporting speed of approval and insufficiently attentive to safety.

3.5 To restore appropriate balance between the FDA's dual goals of speeding access to innovative drugs and ensuring drug safety over the product's lifecycle, the committee recommends that Congress should introduce specific safety-related performance goals in the Prescription Drug User Fee Act IV in 2007.

HOLD INDUSTRY AND RESEARCHERS ACCOUNTABLE FOR MAKING DRUG SAFETY STUDY RESULTS PUBLIC

The committee believes strongly in the importance of increasing the availability of information to the public and to researchers about risks and benefits, whether specific study results or CDER staff analyses of concerns. The National Library of Medicine hosts a website for registration of clinical trials, but with few exceptions, this is voluntary and does not include a summary of results.

4.11 To ensure that trial registration is mandatory, systematic, standardized, and complete, and that the registration site is able to accommodate the reporting of trial results, the committee recommends that Congress require industry sponsors to register in a timely manner at clinicaltrials.gov, at a minimum, all Phase 2 through 4 clinical trials, wherever they may have been conducted, if data from the trials are intended to be submitted to the FDA as part of a new drug application, supplemental new drug application, or to fulfill a post market commitment. The committee further recommends that this requirement include the posting of a structured field summary of the efficacy and safety results of the studies.

APPROPRIATE ADEQUATE RESOURCES FOR DRUG SAFETY

An agency whose crucial mission is to protect and advance the public's health should have adequate resources to do its job. Also, the effect on CDER's work of CDER's overdependence on PDUFA funding with restrictions on how FDA can use the money from user fees hurts FDA's credibility and may affect the agency's effectiveness.

7.1 To support improvements in drug safety and efficacy activities over a product's lifecycle,

the committee recommends that the Administration should request and Congress should approve substantially increased resources in both funds and personnel for FDA. The committee favors appropriations from general revenues, rather than user fees, to support the full spectrum of new drug safety responsibilities proposed in this report.

STABILIZE THE LEADERSHIP OF FDA

Instability in the Office of the Commissioner has been a serious problem for FDA and CDER in particular. A large, complex, science-based regulatory agency cannot perform optimally in the absence of stable, capable leadership, and clear, consistent direction.

3.1 The committee recommends that the Federal Food, Drug, and Cosmetic Act be amended to require that the FDA Commissioner currently appointed by the President with the advice and consent of the Senate also be appointed for a 6-year term of office. The Commissioner should be an individual with appropriate expertise to head a science-based agency, demonstrated capacity to lead and inspire, and a proven commitment to public health, scientific integrity, transparency, and communication. The President may remove the Commissioner from office only for reasons of inefficiency, neglect of duty, or malfeasance in office.

IMPROVE FDA'S COMMUNICATION TO THE PUBLIC

The public would benefit from more information about how drugs are studied before FDA approval, how drugs' risks and benefits are assessed, and what FDA review entails. Patients also need timely information about emerging safety concerns or about a drug's effectiveness in order to make better decisions in collaboration with their health care providers. FDA does not have an adequate mechanism for seeking and receiving specific scientific and patient/consumer advice on communication matters.

6.1 The committee recommends that Congress enact legislation establishing a new FDA advisory committee on communication with patients and consumers. The committee would be composed of members who represent consumer and patient perspectives and organizations. The advisory committee would advise CDER and other centers on communication issues related to efficacy, safety, and use during the lifecycle of drugs and other medical products, and it would support the centers in their mission to "help the public get the accurate, science-based information they need to use medicines and foods to improve their health."

OTHER RECOMMENDATIONS OF PARTICULAR INTEREST TO CONGRESS

3.4 The committee recommends that CDER appoint an Office of Surveillance and Epidemiology staff member to each New Drug Application review team and assign joint authority to Office of New Drugs and OSE for postapproval regulatory actions related to safety.

4.10 The committee recommends FDA establish a requirement that a substantial majority of the members of each advisory committee be free of significant financial involvement with companies whose interests may be affected by the committee's deliberations.

5.4 The committee recommends that FDA evaluate all new data on new molecular entities no later than 5 years after approval. Sponsors will submit a report of accumulated data relevant to drug safety and efficacy, including any additional data published in a peer reviewed journal, and will report on the status of any applicable conditions imposed on the distribution of the drug called for at or after the time of approval.

FOR MORE INFORMATION...

Copies of *The Future of Drug Safety: Promoting and Protecting the Health of the Public* are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington Metropolitan area); Internet, http://www.nap.edu. The full text of this report is available at http://www.nap.edu.

This study was supported by funds from the Food and Drug Administration, the Agency for Healthcare Research and Quality, the Centers for Medicare and Medicaid Services, the U.S. Department of Veterans Affairs, and the National Institutes of Health. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

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COMMITTEE ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYSTEM

SHEILA P. BURKE, M.P.A., R.N. *(Chair)*, Deputy Secretary and Chief Operating Officer, Smithsonian Institution; **DAVID BLUMENTHAL, M.D., M.P.P.,** Samuel O. Thier Professor of Medicine and Health Policy, Harvard Medical School; Director, Institute for Health Policy, Massachusetts General Hospital/Partners Health Care System; **SIR ALASDAIR BRECKENRIDGE, C.B.E.,** Chairman, Medicines and Healthcare products Regulatory Agency (United Kingdom); **R. ALTA CHARO, J.D.,** Warren P. Knowles Professor of Law & Bioethics, University of Wisconsin-Madison; Visiting Professor of Law, University of California, Berkeley; **SUSAN EDGMAN-LEVITAN, P.A.,** Executive Director, John D. Stoeckle Center for Primary Care Innovation, Massachusetts General Hospital; **SUSAN S. ELLENBERG, Ph.D.,** Department of Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine; **ROBERT D. GIBBONS, Ph.D.,** Director, Center for Health Statistics, University of Illinois at Chicago; **GEORGE HRIPCSAK, M.D., M.S.,** Professor of Biomedical Informatics, Vice Chair, Department of Biomedical Informatics, Columbia University; **DAVID KORN, M.D.,** Senior Vice President, Division of Biomedical and Health Sciences Research, Association of American Medical Colleges; **DAVID MELTZER, M.D., Ph.D.,** Section of General Internal Medicine, University of Chicago; **WOODROW A. MYERS, JR., M.D., M.B.A.;** Former Executive Vice President and Chief Medical Officer, WellPoint Inc.; **MARY OLSON, Ph.D.,** Associate Professor of Economics and Political Economy, Tulane University; **BRUCE M. PSATY, M.D., Ph.D.,** Professor, Medicine & Epidemiology, Co-director, Cardiovascular Health Research Unit, University of Washington; **CHRISTOPHER SCHROEDER, J.D.,** Charles S. Murphy Professor of Law, Public Policy Studies Director, Program in Public Law, Duke Law School; **ANDY STERGACHIS, Ph.D., R.Ph.,** Professor of Epidemiology & Adjunct Professor of Pharmacy, Interim Chair, Pathobiology, Northwest Center for Public Health Practice, School of Public Health & Community Medicine, University of Washington.

IOM STAFF

KATHLEEN STRATTON, Ph.D., Study Director; **ALINA BACIU, M.P.H.,** Program Officer; **AMY GROSSMAN, M.P.H.,** Senior Health Policy Associate; **RUTH KANTHULA, M.P.H.,** Senior Project Assistant; **ROSE MARIE MARTINEZ, Sc.D.,** Board Director, Board on Population Health and Public Health Practice; **GEORGE ISHAM, M.D., M.S.,** Liaison, Board on Population Health and Public Health Practice.

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EU plan may let drug firms sidestep ban on advertising

Sarah Boseley, health editor
The Guardian, Tuesday April 8 2008

Drug companies will be allowed to sidestep the ban on advertising drugs to the public under new European proposals, consumer groups warned yesterday.

The European commission plans to allow drug companies, which have a history of failing to warn about the risks of their medicines, to give "information" about their drugs to the public on TV, the internet and in print.

While consumer groups agree that better information is needed, they say one-sided information from a drug company is little more than advertising. They warn that companies which have failed to warn of the risks of drugs such as the painkiller Vioxx, which caused heart attacks, and Seroxat, which can make young people feel suicidal, cannot be trusted as sources of unbiased information.

"The proposal is clearly driven by the pharmaceutical industry's commercial concerns - not by the interests of patients," said the Picker Institute, an authority on patient-centred healthcare, in its response to the commission.

Patients needed to be able to choose between treatment and no treatment as well as between different drugs, and sometimes between drugs and surgery. "These proposals specifically exclude comparative information," said Don Redding of the institute. "The plans enable companies to push information direct to patients and to use all available media to do that."

The consultation document from the enterprise and industry directorate-general says: "It should be possible for the pharmaceutical industry to disseminate information on prescription-only medicines through TV and radio programmes, through printed material actively distributed, through information in printed media or through audiovisual and written material provided to patients by healthcare professionals."

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