EXAMINATION OF THE PHARMACEUTICAL INDUSTRY, ...IMENTS 1973–74

JOINT HEARINGS

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ...BOR AND PUBLIC WELFARE

AND THE

SU...ITTEE ON ADMINISTRATIVE PRACTICE AND PROCEDURE

OF THE

COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

NINETY-THIRD CONGRESS

FIRST AND SECOND SESSIONS

ON

S. 3441 and S. 966

LEGISLATION AMENDING THE PUBLIC HEALTH SERVICE ACT AND THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

PART 7

AUGUST 15 AND 16, 1974

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EXAMINATION OF THE PHARMACEUTICAL INDUSTRY, 1973–74

THURSDAY, AUGUST 15, 1974

U.S. SENATE,
SUBCOMMITTEE ON HEALTH OF THE
COMMITTEE ON LABOR AND PUBLIC WELFARE,
AND THE SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE
AND PROCEDURE OF THE COMMITTEE ON THE JUDICIARY,
Washington, D.C.

The subcommittees met, pursuant to notice at 10:10 a.m., in room 4232, Dirksen Senate Office Building, Senator Edward M. Kennedy [chairman of the subcommittees] presiding.

Present: Senators Kennedy and Javits.

Committee staff members present: LeRoy G. Goldman, professional staff member and Jay Cutler, minority counsel.

Senator KENNEDY. The subcommittees will come to order.

OPENING STATEMENT OF SENATOR KENNEDY

Senator KENNEDY. This phase of the drug hearings will be a joint venture between the Health Subcommittee and the Subcommittee on Administrative Practice and Procedure of the Senate Judiciary Committee.

Today, the subcommittees begin the second, and perhaps most important phase of its investigative and legislative inquiry into the drug industry.

The first phase focused on the advertising, marketing, and promotion of prescription drugs currently on the market. This phase will explore the process by which new drugs are researched, developed, and approved for marketing in the United States.

As part of this phase, the subcommittees will take a long and hard look at the way the Food and Drug Administration (FDA) operates. It is that Agency upon which the American people depend to assure the safety and effectiveness of all their drugs.

Critics contend that it is also the agency whose policies restrict the rate at which significant new drugs are developed and the agency whose go slow policies deprive the American people of treatments which are available much earlier in many other countries.

Other critics contend that there is no drug lag in the United States; that the real danger to the health of the American people is the laxity with which the 1962 Food, Drug, and Cosmetics Act Amendments are being administered.

These critics contend that drugs are tested in humans before adequate animal testing is complete, and that unsafe and ineffective drugs still find their way onto the market.

These hearings will attempt to sort out the facts, and determine whether additional legislation is required.

The Subcommittee on Administrative Practice and Procedure will look at the functioning of a number of government regulatory agencies in the months ahead; staff has been exploring the operations of the Food and Drug Administration for several weeks. And that subcommittee will look for administrative responses to a number of items considered at these hearings.

I consider these hearings to be of prime importance.

From my own experience, I know how the hopes of millions of Americans ride on the development of significant new drugs—to combat cancer, to help control heart disease, to really cure diabetes. The list of needs is endless.

The task before our Nation's researchers, in both the public and private sectors, is both difficult and extraordinarily important. Yet, I also know the dangers of premature marketing of unsafe and ineffective drugs, of premature experimentation on vulnerable population groups.

We are looking for the proper balance between the needs of scientists to pursue promising leads and the needs of the American public to be sure that marketed drugs are safe and effective, and have been developed pursuant to well-controlled research that places its human test subjects at the least possible risk.

Today, we will hear from two panels of witnesses. The first consists of 10 present and 1 former employee of the Food and Drug Administration. They are all appearing pursuant to subpenas issued by the Administrative Practice and Procedure Subcommittee. They did not seek the committee out. The subcommittee sought them out after reviewing FDA files for many weeks.

I expect that no administrative action will be taken against any of these employees. And, today, I intend to make that specific point in a letter to the FDA Commissioner, Dr. Alexander Schmidt.

The second panel consists of three outside consultants to the Food and Drug Administration (FDA), all of whom have worked on drugs that have been the responsibility of one or more of our witnesses.

We look forward to your testimony.

I am going to ask all of the witnesses to rise and be sworn before the committee, if you would, please.

I swear to tell the truth and nothing but the truth, so help me, God.

[All witnesses listed on first panel were duly sworn.]

Senator KENNEDY. I am just going to read a word of introduction about each of the witnesses here this morning, starting with Dr. Appleton.

A review of the credentials of these witnesses would indicate extraordinary backgrounds in the field of education, in research, as medical doctors, many years working for the Food and Drug Administration.

They are a highly competent group who have served and are serving in the FDA in a variety of different capacities.

Dr. B. L. Appleton has been employed by FDA as a chemist since 1963. Prior to that, he was employed in the research departments of General Foods and Armour Corp. He obtained his Doctorate in Chemistry from Indiana University, and did 2 years postdoctoral studies at the University of Louisville.

Dr. John O. Nestor is a certified Pediatric Cardiologist who has been employed as a medical officer at FDA since 1961. He is a board certified pediatrician with a subspecialty of pediatric cardiology. He is a graduate of Georgetown University School of Medicine. He served as a flight surgeon in the Air Force in World War II. Prior to joining FDA, he was in private practice. He has served as a consultant in pediatric cardiology to the National Heart Institute and the Arlington (Va.) Hospital, and as an assistant professor of pediatrics at Georgetown and associate professor of pediatrics at Howard Universities. He was chief of the pediatric cardiology clinic at the Alexandria Community Health Center in Alexandria Hospital.

Dr. David Lidd has been employed as a medical officer at FDA since 1963. He graduated from the State University of New York College of Medicine (downstate), and was an intern at Syracuse University and a resident in pediatrics at the Children's Hospital in Buffalo. He then was in private practice as a pediatrician for approximately 6 years, followed by training in allergy at Montefiore Hospital in Pittsburgh and in immunology at the University of Pittsburgh School of Medicine. He then returned to private practice until he joined FDA. He is certified as a pediatrician, allergist, and immunologist.

Dr. J. Marion Bryant has been a medical officer at FDA since 1967. For 10 years prior to that, he was attending physician and chief of cardiology at the Knickerbocker Hospital in New York City, chief of the 4th Medical Division of Hypertension Clinic at Bellevue Hospital and associate attending physician at the New York University Medical Center. He is a graduate of the University of Virginia Medical School. He also was an associate professor of medicine at the New York University School of Medicine and the New York University Postgraduate Medical School.

Dr. John Winkler has been a medical officer at FDA since 1959. He is a graduate of Georgetown University Medical School following which he interned at Providence Hospital in the District of Columbia. He served 2 years in the Air Force and then did his residency in Internal Medicine at Providence Hospital.

Dr. Carol Kennedy is currently employed as a medical officer in psychiatry in the Bureau of Hearings and Appeals of the Social Security Administration. She was a medical officer at FDA from 1970 to May 1974. She is a graduate of the University of Miami Medical School, and took her psychiatric training at the University of Tennessee. She specialized in pediatric psychiatry and, prior to joining FDA, was the director of the Memphis-Shelby County Mental Health Center for Children. She was also in the private practice of psychiatry, specializing in children and adolescents.

Mrs. Frances D'Acosta has been employed as a pharmacologist at FDA since 1964. She is a graduate of Howard University and took graduate work at the Howard University School of Medicine and Catholic University in Bacteriology. She received her master's degree from the Department of Pharmacology at Howard University. Prior

to joining FDA, she was employed as a pharmacologist at the National Heart Institute of the NIH.

Dr. Alice Campbell has been employed as a medical officer at FDA since 1969. She is a graduate of the University of Vienna Medical School. She interned in medicine and surgery at the Huron Road Hospital in Cleveland, Ohio, and took a 3-year psychiatric residency at the Cleveland Psychiatric Institute and Clinic. She then went into private practice as a psychiatrist in Cleveland and later in Maryland. Prior to joining FDA, she was a psychiatrist at St. Elizabeths Hospital in Washington, D.C.

Dr. John Gerda has been employed as a medical officer at FDA since 1966. He is a graduate of the Cornell University Medical School, and interned at George Washington University Hospital. He then took his residency in surgery at the University of Wisconsin Medical School. Prior to joining FDA, he was a staff surgeon at St. Elizabeths Hospital in Washington, D.C.

Dr. Robert Knox has been a medical officer at FDA since 1963. Prior to that, he was in private practice in Denver, Colo. Dr. Knox is a graduate of Georgetown University Medical School. He interned at the U.S. Marine Hospital in Cleveland, Ohio, and took his residence in internal medicine at the Colorado General Hospital in Denver. He then took an additional 2-year residency in internal medicine at the VA Hospital in Denver, followed by two additional years residency in internal medicine at the VA Hospital in Grand Junction, Colo.

Dr. Philomen Ciarla has been employed as a medical officer at FDA since 1969. He is a graduate of the New York Medical College, and interned at the Homeopathic General Hospital in East Orange, N.J. He then went into private practice until he joined the Public Health Service in 1941, where he served until his employment by FDA.

This supports my earlier observation about the wealth of experience and background that our panel has this morning, and we are looking forward to their testimony.

I want to point out to the witnesses at the outset that we are not interested in any trade secrets. We are not interested in any of the claims of confidential matters to you that would directly affect particular drug companies.

We are interested in the broader issues which, I think, will be developed during the course of our hearing this morning. We are interested in the way the procedures have an impact on you who have in common your reviewing of new drugs, and what your experiences have been in that area.

Also, we want to talk a little bit about the kind of research that has been done on animals, and whether it has been sufficient, and also about the "me too" drugs, and what is happening in that area.

We will start off now with Dr. Appleton. We are going to ask the different members of the panel some of their impressions as we run through common themes so we will be calling on you at different times, but we want to begin with Dr. Appleton.

Perhaps you could describe just for our record the role of the medical officer.

[Dr. Appleton shook his head negatively.]

Senator KENNEDY. Let us ask Dr. Nestor that.

Would you tell us the role of the medical officer and the primary reviewing team at the FDA?

STATEMENT OF JOHN NESTOR, M.D.; ALICE CAMPBELL, M.D.; CAROL KENNEDY, M.D.; J. MARION BRYANT, M.D.; MRS. FRANCES D'ACOSTA; JOHN GERDA, M.D.; PHILOMEN P. CIARLA, M.D.; DAVID LIDD, M.D.; JOHN WINKLER, M.D.; B. L. APPLETON, PH. D.; AND ROBERT KNOX, M.D., A PANEL

Dr. NESTOR. I assume that you are referring to the medical officer who is reviewing new drugs.

Senator KENNEDY. That is correct.

Dr. NESTOR. In essence, what happens is when an application comes in, it consists of three basic parts—chemistry, pharmacology, and the medical data.

A chemist reviews the chemistry. A pharmacologist reviews the pharmacology, and a medical officer reviews the clinical data. Then he puts the whole thing together, taking the reports of the pharmacologist and the chemist, and comes up with an opinion and a recommendation.

He does not make any final decision. He only makes a recommendation to his superiors. This is the way it should work ideally. It does not always work this way.

Senator KENNEDY. When it works well, it can obviously have an extraordinarily important positive and therapeutic effect. I think many of us remember your very instrumental work on MER–29, in keeping that off the market, and perhaps you would review very briefly with us your experience with that.

Dr. NESTOR. I think I can.

It took a period of several years but, in essence, this drug went on the market with not only grossly inadequate animal studies to substantiate introducing the drug in humans, but, as we subsequently learned, much of the data was falsified or completely withheld from the Food and Drug Administration.

But even with the data that were falsified and withheld, there was enough in the new drug application to clearly indicate that this drug should never have gone on the market. This was subsequently admitted by Deputy Commissioner John Harvey publicly after the event, and after the skullduggery was uncovered.

I think I should say that the main things it caused in humans were cataracts and very severe skin conditions, adrenal cortical hypofunction, impotence, and some other minor side effects.

It turned out eventually that the two firms involved and three executives of the firms were indicted on 12 counts by a Federal court, and they pleaded nolo contendere.

The two firms were fined the maximum of $8,000. The three executives who were responsible for the fraudulent data, and the withholding of data, were given a 6 months probation, in which they did not even have to report to the court.

Subsequently, there was a total of $338 million in suits against these companies, which it is estimated were finally settled for around $50 million.

It is also interesting that at the time the first warning letter went out from the Food and Drug Administration on December 1, 1961, the stock of this company was $108 with 9 million shares out.

By the time it came off the market in April 1962, the stock had fallen somewhere around $42, so that there was a paper loss to the stockholders of something like $600 million.

Senator KENNEDY. I think the Thalidomide story is familiar to all Americans, and I understand you received a commendation from the Assistant Attorney General of the United States for your work, did you not?

Dr. NESTOR. No.

That was for MER–29. I did work with Dr. Kelsey on the Thalidomide matter just peripherally, but the commendation from the Assistant Attorney General and from the grand jury was on the MER–29 work. I spent 13 months working as a consultant, and as a witness for that grand jury.

Senator KENNEDY. For the work on the MER–29, you received a letter of commendation, as I understand?

Dr. NESTOR. I did.

Senator KENNEDY. Did you ever get any commendation from the FDA?

Dr. NESTOR. No. As a matter of fact, I got nothing but harassment from the head of FDA.

Senator KENNEDY. What kind of harassment?

Dr. NESTOR. Well, for one thing, they attempted to deny me an in-grade step raise which would have meant a few hundred dollars. And in order to have that corrected, I literally had to threaten to go before the grand jury and claim that I was being harassed in order for the Food and Drug Administration to reverse this.

Another thing that happened was that I used to come back from the courthouse every day at noon—we were, at that time, located in what was called Tempo S, and I would come back to see my mail every noon and keep up on the new drug applications that had been assigned to me, so that no new man would have to take over. I could obviously settle things in 5 minutes when someone else might have to review the whole application.

I came back one day and found my office empty, found all my furniture gone. I found out that I had been transferred to a completely different branch of the division, without being informed or consulted. This is just an idea.

Senator KENNEDY. Were you given any reason for your transfer?

Dr. NESTOR. I was not consulted or given any reason or informed. I came back and found I was transferred.

Senator KENNEDY. Can you tell us, under the current system, a little bit about how the process works when you want a new drug approved after you review it?

Dr. NESTOR. You must realize that I was transferred out of the New Drug Division in March of 1972, against my violent objections, and I have not processed new drugs since that time.

As a matter of fact, I have not done 3 months of work in the last 2½ years, and the taxpayer is pay me $36,000 a year. And I have not done the work simply because it has not been given to me.

Senator KENNEDY. Maybe you can tell us a little about the process of what takes place after you have reviewed it in the current system.

Do you work as part of a team?

Perhaps I can ask Dr. Lidd.

Dr. LIDD. Yes, Senator, I do work as part of a team.

What one looks at in terms of the role of the medical officer is to determine, first of all, whether there are any chemistry or pharma-

cological problems that would preclude one from making inferences with respect to safety and efficacy of the drug.

When those aspects are clarified, speaking from my personal experience, what I do is look at these three things:

One is, what is the disease one is treating? Is it a self-limiting disease, or is it beset with multiple sequelae?

Two, what are the other drugs that are available with respect to the benefit-risk assessment?

Three, what is the benefit-risk assessment with respect to the given drug?

There is a value judgment to be made here, namely the more serious the disease, the more risk one will accept. The less advantageous the drug, the less risk one will take to obtain a given amount of benefit.

Senator KENNEDY. Once you have approved a particular drug, what happens next?

Dr. LIDD. Then the decision is moved up to, shall we say, the group leader and the division director within the particular organization, and subsequently it goes up to finally, I believe, the Director of the Bureau. And then after that, to the Commissioner's office.

Senator KENNEDY. Have you every made a recommendation to approve a drug which has been overturned?

Dr. LIDD. No, sir.

Senator KENNEDY. I would like to ask Dr. Bryant that particular question.

Have you ever made a recommendation for approval of a drug that has been overturned at a higher level?

Dr. BRYANT. No, sir.

Senator KENNEDY. Dr. Gerda?

Dr. GERDA. Yes, I have.

Senator KENNEDY. You have?

Dr. GERDA. Yes. I made some adverse recommendations on drugs which subsequently were overruled.

Senator KENNEDY. I am sorry. I am not asking on recommendations that have been overruled, but whether you ever recommended approval of a drug and were overruled.

Dr. GERDA. I am sorry. No.

Senator KENNEDY. Dr. Campbell? Or any of you?

[There was a general negative response.]

Senator KENNEDY. How about the reverse situation?

We will go back to Dr. Lidd.

Have you ever had a drug that you have recommended for disapproval overruled at a higher level?

Dr. LIDD. I would like to qualify that.

I have recommended that there was insufficient evidence for approval, sir.

Senator KENNEDY. What about the rest? Dr. Gerda?

Dr. GERDA. Yes, that was what I was referring to previously.

Senator KENNEDY. Dr. Bryant?

Dr. BRYANT. Yes.

Senator KENNEDY. Dr. Winkler?

Dr. WINKLER. Yes.

Senator KENNEDY. And all the others, yes?

[There was a generally affirmative response.]

Senator KENNEDY. Dr. Bryant, could you tell us why the FDA should not have the same kind of tests for both approval or disapproval?

Dr. BRYANT. Your question is why?

Senator KENNEDY. Yes.

Dr. BRYANT. Well, I am not able to state exactly why without giving you just an opinion.

Some of the drugs that I have recommended not be approved because there was, in my findings, inadequate evidence of efficacy and of safety, these drugs have been approved, but the reason why, I do not know except that it has been presented that it is a matter of opinion, and medical opinion varies, they say.

Senator KENNEDY. Is it a question that medical opinion may differ, but it appears that it has only been exercised when you do not approve it rather than when you do?

Could you not be wrong when you are approving it as well as when you disapprove it?

Dr. BRYANT. Certainly.

Senator KENNEDY. But I gather from what you have testified here that your medical judgment has not been challenged when you approve. It is only when you disapprove that it has been second-guessed?

Dr. BRYANT. That is correct.

Senator KENNEDY. Can you tell us why you think that has been so?

Dr. BRYANT. I would have to speculate so far as the reason why. The only thing I can report to you is my experience, and that is that it is a very uncomfortable experience one finds himself in when he recommends non-approval of a drug.

One gets criticized and more or less buffeted around from one administrator to the other.

It is the administrators who have to do with the approval of drugs, acting on the recommendations of the medical officer. The medical officer does not approve or disapprove new drugs, as Dr. Nestor has already pointed out.

Senator KENNEDY. What sort of raw material is available to the administrator that is not available to you to enable him to make a judgment which you are not able to make?

Dr. BRYANT. Again, that is a difficult question to answer. The administrators sometimes have meetings with the sponsor; that is, the representatives of the drug company to which the medical officers are not privy. I cannot speak for what goes on in the meetings that I have not attended.

Senator KENNEDY. You mean the administrators would meet with the drug companies when the medical officer, who is doing the review on the particular item, would not be present?

Has that ever happened to you?

Dr. BRYANT. Yes. In some instances, not always, but that happens not infrequently.

Senator KENNEDY. Is that true of the rest of the panel? In your own personal experience, has that happened to you?

Dr. KENNEDY. Yes.

Dr. CAMPBELL. Yes.

Mrs. D'ACOSTA. Yes.

Senator KENNEDY. Let us see if we can become somewhat more specific on Hexobendine. Could you tell your experiences with that

particular drug? This has been marketed overseas first, as I understand.

Dr. BRYANT. Senator, would it be permissible, since you have asked other people here about how they review a drug, if I give you a very short statement as to how I approach it?

Senator KENNEDY. Yes.

Dr. BRYANT. The sponsor, that is the drug company that submits the drug, submits certain claims for it. I familiarize myself with those claims and then review the raw data, in other words review as much as possible actually what was done, and what happened, rather than blindly accepting the opinions of either the investigators or the opinion of the sponsor.

I base my evaluation on whether or not the raw data is supportive of the claims that the drug company makes. In regard to the particular drug that was just mentioned—and I hope here that I am not in violation of any aspect of the act that pertains to "trade secrets"—but if I approach that, would you be so kind as to stop me; in other words, to serve as my lawyer under the circumstances? [Laughter.]

Senator KENNEDY. We will do the best we can.

As you understand, we are not interested in particular trade secrets, but you are responding to questions from us. And I think the record will reflect that. You are trying to give us an honest answer on it, and that is what we appreciate.

Dr. BRYANT. In the 7, going on 8 years that I have been with the Food and Drug Administration, I have never been able to get a clear picture of what the Food, Drug, and Cosmetics Act means when it refers to trade secrets. Neither have I been able to get a clear picture of the philosophy or the policy of the Food and Drug Administration as to their interpretation of that. This is an area in which I am not at all sure of myself.

But, to go back and to answer your question about Hexobendine, this was a drug that was developed for the treatment of several ailments, one of them angina pectoris, heart pain in other words, for the symptomatic relief of that ailment; cerebral vascular insufficiency, in other words, misfunction of the brain following a stroke, or an impending stroke; and, insufficiency of the arterial circulation through the peripheral arteries, those of the legs in particular.

To make a long story short, this drug was investigated in several hundred human subjects under an investigational new drug (IND) for about 4 years before adequate animal testing was done, which showed that it uniformly and rather quickly caused the appearance of cataract in dogs. However, this was not carried out until after approximately 4 years of testing in humans.

Incidentally, this drug's IND has been inactivated on the part of the drug company. They withdrew it, but I am informed by the company that it is marketed in a number of countries all over the world. Maybe you might like to ask me more specific questions.

Senator KENNEDY. I would like to ask you whether there were humans who were taking this drug prior to the time there had been adequate animal testing?

Dr. BRYANT. I have not reviewed this recently so I cannot give you precisely the number of humans treated because I am not prepared for any of these specific questions, but it was several hundred patients.

Some were inmates of prisons who had received this drug prior to adequate testing on animals.

Senator KENNEDY. Is that appropriate? Is that right?

Dr. BRYANT. In my opinion, it is most inappropriate. It is in violation of the whole philosophy of what we might call the "scientific method" that has been enacted into law in the Food, Drug, and Cosmetics Act.

Senator KENNEDY. Let me ask the other members of the panel.

Dr. Nestor, what has been the adequacy of animal testing prior to the time of application upon human beings, based upon your experience?

Dr. NESTOR. If I were asked what the greatest fault of the Food and Drug Administration is——

Senator KENNEDY. I am not asking you that.

Dr. NESTOR. That is what I am getting to. It is exactly this, that we are not requiring drug companies to do adequate studies, adequate toxicity studies, to complete them and evaluate them before they are given to humans. If we had done this, we can cite case after case where no single human subject would have gotten the drug.

The problem is we are doing almost simultaneously and concurrently animal and human studies side-by-side, and by the time the animal shows severe toxicity, several hundred humans have usually been exposed.

We can give you specific drugs. As a matter of fact, I took this very problem to Commissioner Edwards on June 11 and 12 of 1970, and for my pains I was detailed out of New Drugs for the first time. So I think this is the greatest single wrong at the Food and Drug Administration right now.

Senator KENNEDY. Dr. Campbell, would you give me your experience on animal testing, and then I will ask Dr. Kennedy the same question.

Dr. CAMPBELL. One of the problems is the FDA has sent out guidelines as to minimal animal testing that has to be done. Unfortunately, however, those guidelines were published in 1966.

Since then, of course, we have learned considerably about the kinds of evidence we can use for human research from animal testing. Those guidelines have not been updated, elaborated or expanded since 1966. Therefore, drug companies are, in fact, in many instances, complying with the FDA guidelines which are in themselves inadequate.

So that is my view as to one of the primary problems regarding animal testing and the elaboration or extrapolation of data from that to humans.

Senator KENNEDY. Your conclusion is that there is inadequate testing in animals?

Dr. CAMPBELL. My conclusion is that the drug companies are complying with the guidelines, but the guidelines have not been updated.

Senator KENNEDY. Has anyone brought that up to the people in FDA, as to whether those guidelines should be upgraded?

Dr. CAMPBELL. As a matter of fact, my situation is somewhat similar to Dr. Nestor's, because I was working on a task force for the use of certain kinds of drugs, behavior altering drugs, and it came to my attention at that time this might be a very good time to bring to the attention of the proper people the fact that these guidelines needed updating. I did so.

I was removed from the task force, and removed from the division into a situation in which I am now a glorified clerk.

Senator KENNEDY. You mean shortly after you suggested to officials in FDA that these guidelines ought to be changed, you were transferred out?

Dr. CAMPBELL. That was not the only reason, but that was one of the recommendations that I did make, that those would need to be updated, and we could go from this particular task force and update the guidelines on animal testing. And I was shortly thereafter removed.

Senator KENNEDY. Doctor Kennedy, back to the animal testing.

Dr. KENNEDY. With respect to the animal testing, there are a couple of areas, ones like Dr. Campbell mentioned.

I was reviewing a specific area of drugs. These were drugs that were used in children. We felt that the animal data for use of the drug in children, the guidelines, were not adequate. Mrs. D'Acosta can give you more specifics on that.

In terms of specific drugs, I can think of one example where an antisensitizing agent was being tested. The animal pharmacology were completely inadequate. The reviewing pharmacologist and I met, decided they were inadequate, presented the deficiencies to the division director, who agreed that these deficiencies did indeed exist.

We met several times with the division director. The reviewing pharmacologist and I met with the drug firm. They were informed of the deficiencies. I was called by the then director of the Office of Scientific Evaluation, whom the drug firm had approached directly, and who informed him that studies could go ahead; that he did not see any problems. We subsequently met with this office director, and he agreed that he would leave that to the decision of the division director.

The division director and the reviewing pharmacologist and I met with the drug firm, and at this time the division director allowed the firm to go ahead anyway. Subsequently, they finally had to, when the deficiencies were repeated again at a later meeting—the firm ended up doing the studies over.

Senator KENNEDY. The studies that you had found were either inadequate or incomplete or had not been done?

Dr. KENNEDY. That is correct.

Senator KENNEDY. Let me get back to Dr. Bryant and Hexobendine. After it was withdrawn from the market here in the United States——

Dr. BRYANT. Excuse me, Senator.

This was never a marketed drug. It was an investigational drug. It was withdrawn from investigation in the United States.

Senator KENNEDY. Was it ever marketed overseas?

Dr. BRYANT. I am informed by the sponsor that it has been marketed in the majority of the countries in the world.

Senator KENNEDY. In where?

Dr. BRYANT. The whole world, w–o–r–l–d.

[Laughter.]

Senator KENNEDY. Do you know if the FDA ever was in contact with any of these other countries regarding the defects?

Dr. BRYANT. To my knowledge, it was not. I am aware of other drugs that we have disapproved in which other countries, namely

Australia, have inquired as to why a drug was not approved. The Food and Drug Administration has responded to those inquiries.

Senator KENNEDY. But we have not initiated contact with other countries?

Dr. BRYANT. To my knowledge, that has never been the policy. I have never even heard it mentioned. It may well be, but not to my knowledge.

Senator KENNEDY. Were you ever pressured by supervisors to change your officials accounts of meetings on this drug?

Dr. BRYANT. Well, I have been.

Senator KENNEDY. You have been what?

Dr. BRYANT. I have been pressured to change my position or my recommendation with regard to the non-approval of other drugs. This generally comes in a not too subtle indirect form of harassment and unpleasant argumentation that is not on a scientific level.

Senator KENNEDY. Is it just discussion? What sort of pressure are you talking about? Let me give you a specific question. Were you ever asked to remove anything from files?

Dr. BRYANT. Yes, I have been asked to remove a memorandum from the files. The one that comes to my memory right off was the memorandum of the advisory committee meeting concerning Hexobendine.

Senator KENNEDY. What would be the purpose of removing material from the file? Was it material that was unfavorable to the drug?

Dr. BRYANT. Things of this sort are generally always unfavorable when they are removed. This particular memorandum that I am referring to was unfavorable.

Dr. KENNEDY. And you were ordered to remove it?

Senator KENNEDY. As a matter of fact, this is a copy of the memorandum which orders you to remove it. I will just read the pertinent paragraph, and we will include that in the record. Attached to this memo is a copy of the official minutes of the advisory committee. This should be inserted into the IND, and your own copy of the minutes are to be removed.

[The memorandum referred to follows:]

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 9/17/73
FROM: E. Q. Bolton		OFFICE OSE
TO: J. Morin Bryant M.D.		DIVISION BD II
SUBJECT: IND - 4196 - Hexobendine		

SUMMARY

I received a telephone call from Dr. O'Dell of Merrell - National Laboratories regarding their letter of July 18, 1973.

In view of the recommendation of the Opthalmology advisory Committee; a letter should issue to the company that the IND is considered withdrawn.

Attached to this memo is a copy of the official minutes of the advisory Committee. This should be inserted into this IND. Your own copy of the minutes are to be removed. If you wish to keep them in your personal file, that is acceptable. The record should only reflect the official minutes.

EQBolton 9/17/73

SIGNATURE	DOCUMENT NUMBER

FORM FDH-2034 (11/65)

Senator KENNEDY. Dr. Kennedy, has this ever happened to you?

Dr. KENNEDY. Not only have I felt the pressure to have my accounts changed, there have been, in fact, significant portions of some of my reviews deleted. I had these typed. They were returned to me, retyped without the pertinent information for my signature, whereupon I have written, "This is not the review I originally made."

These comments were typed over, and again sent to me for my signature. And when I refused to sign, I assume they went to the file. I might add that the portions which were removed in one case referred to a conference that was background information which was routine—I think most medical officers have included background information.

There did not happen to be a memorandum of the conference in the file, so I put the comments in. Another portion which was removed was specific safety data which also happened to include the fact that I had previously brought this question of safety to the attention of the Division Director, and this portion was removed.

Senator KENNEDY. Is this scientific material that was being substituted?

Dr. KENNEDY. No. It is just simply deleted.

Senator KENNEDY. This was, as you pointed out, unfavorable information, at least based upon your own scientific conclusions of studies of particular drugs?

Dr. KENNEDY. Yes. And in one particular instance, it was a specific question on safety. It was another drug that was used in children.

Senator KENNEDY. Was that Tofranil?

Dr. KENNEDY. No. It is a little different from Tofranil. It was another, Norpomine, which is like Tofranil, and the questions have been raised concerning both drugs.

Senator KENNEDY. Did you have a similar experience with other drugs?

Dr. KENNEDY. With Tofranil, for example, for it is used in bed wetting. A previous medical officer had this drug to review first, and she turned it down. She was overruled by the Division Director and, subsequently, I received the drug.

Mrs. D'Acosta and I both worked on the drug. She was the pharmacologist for most of the drugs that were used in children. We had in-house meetings with the reviewing teams.

Dr. Allen K. Done happened to be the Special Assistant to the Director on Pediatric Drugs. We brought up the fact that the drug had previously been turned down by the previous medical officer. We pointed out that his findings showed that the drug's efficacy had not been clearly demonstrated.

Mrs. D'Acosta pointed out that the pharmacology questions in terms of the drug being used in children were not satisfactory. I pointed out questions on safety. We had other conferences on it.

Eventually, when I wrote up my review, an additional statistical analysis was gotten, and I was told I was not to review that. The drug was removed from me.

It went up with my recommendation, in which the Division Director concurred. However, it was subsequently returned by the office since part of my recommendations had not been included.

The previous notes which had been made on the bottom of my review were then altered to indicate that the Division Director really did not agree with what I had to say after all.

Senator KENNEDY. That was put in the record?

Dr. KENNEDY. The interesting thing—and the thing that disturbed me about this—is I never saw any of this. I just happened to see it on a card that was going up to the Director of the Office of Scientific Evaluations. Otherwise, I would never have seen that information. I would never have known.

Senator KENNEDY. That this was being changed or altered?

Dr. KENNEDY. That this was being done.

Senator KENNEDY. Which was clearly either a misrepresentation or contrary to your own scientific study?

Dr. KENNEDY. Yes.

Senator KENNEDY. Dr. Bryant, could you tell us a little bit about Dilantin, about what your experience was?

Did you approve its standard usage for irregularity of the heart beat?

Dr. BRYANT. Simply, Dilantin is one of the classical drugs of the world. It is the drug for the treatment of epilepsy.

Application had been made to expand its use for the treatment of irregularities of the heartbeat, and I recommended that it not be approved for that use, due to the fact that there was a great lack of information; that is, raw data, namely electrocardiograms. I could look at the electrocardiographic tapes themselves and see what was going on, rather than have to take someone else's interpretation or, if I might use the word here, if you will excuse me, transcripts of those tapes. That was the basis on which I recommended nonapproval.

Now, I did not take the position that this drug is not safe and efficacious for the treatment of arrhythmias. My position was that the sponsor had failed to substantiate his claim that it was safe and efficacious, as the law requires.

Senator KENNEDY. What happened shortly after you made these recommendations? Were you transferred?

Dr. BRYANT. Yes. But it is hard for me to date my transfer to that specific action, because there were so many similar ones that I had taken part in, that it would be very difficult to say which was what. And I was never informed anyway.

By the way, I first made that recommendation, if my memory serves me correctly, about 4 years ago. It just kept bouncing around and bouncing around, and it seemed as if my recommendation was never confirmed by the Administration or disproven by the Administration.

It was just kind of shelved. Then, periodically, it would reappear.

The last time it reappeared, I was requested to present it to one of our advisory committees, and as a result of that presentation, it seemed to me at the time that all of the members of the advisory committee agreed with my nonapproval recommendation.

Officially, I have never been informed as to what that advisory committee concluded, although this advisory committee met almost 2 months ago. And according to some of the requirements, a report of this decision of the committee is supposed to be sent to the Commissioner within about 48 hours. And I would assume that documentation would be supplied to the file of that.

I have heard unofficially as to what their conclusions were and their recommendation was, which I do not feel free to verbalize here.

Senator KENNEDY. We are not asking for that.

Gathering from what both you and Dr. Kennedy have said, it does not appear to me that you get access again to these files once they move out of your department. Then, almost instantaneously, you are cut out of the ultimate decisionmaking.

Dr. KENNEDY. In many instances, sometimes we are aware of what happens because we are involved to a certain point. In a particular drug I discussed before, for example, we had asked for additional labeling changes in complication of adverse reaction, questions on safety, to the drug firm.

I was involved in that preparation of the letter. However, when the drug firm came in to discuss this, they met with the division director alone, and I was not included in that. In fact, the drug representative was very surprised, because he thought I was going to be in that meeting.

Senator KENNEDY. Dr. Bryant, just before we move on, you were Chief of cardiology of the Knickerbocker Hospital in New York.

Dr. BRYANT. Yes.

Senator KENNEDY. And the chief of the hypertension clinic at Bellevue Hospital in New York.

Dr. BRYANT. Actually, that was an NYU Postgraduate Division at Bellevue Hospital, and I was in charge of cardiology, the Fourth Medical Division, Bellevue Hospital.

Senator KENNEDY. And now you have been removed from the cardiovascular-renal division at the FDA?

Dr. BRYANT. That is correct.

Senator KENNEDY. Is that not your primary area of expertise?

Dr. BRYANT. I had spent almost 30 years in that specialty of cardiology, and had really devoted my whole life to it.

Senator KENNEDY. Where are you working now?

Dr. BRYANT. I am presently assigned to the Generic Drug Staff, which has to do with abbreviated NDA's (new drug applications).

This is a speedup at the Food and Drug Administration which it has taken on just recently, so that particular "me too" drugs would not have to go through the whole rigamarole of proof of safety and efficacy.

Senator KENNEDY. Are you reviewing any drugs now that are related to the cardiorenal field?

Dr. BRYANT. I have spent a good deal of my time since I have been there helping out, and I do not know why, on this Dilantin presentation for the advisory committee.

Senator KENNEDY. But other than that?

Dr. BRYANT. I am not specifically working with cardiac drugs, in other words, if that is what you are referring to.

Senator KENNEDY. It seems that is your expertise. I am sure you are enormously gifted in many areas, but you have spent 30 years of your life working in this area. And I understand now you have been transferred out of that section, and you are working in an area that does not relate to the evaluation of cardiorenal drugs.

Dr. BRYANT. There is some relation, but it is a minor relation, and

I might explain that I am not in a position where I have the opportunity to look at raw data.

I am looking purely at the transcripts and not the raw data themselves.

Senator KENNEDY. Before leaving this subject, how many of you on this panel have been transferred out of your areas of primary training?

[Drs. Knox, Gerda, Campbell, Kennedy, Bryant, Nestor, and Lidd indicated affirmatively.]

Senator KENNEDY. Dr. Winkler, you seem to be about the only one. Have you been transferred at all?

Dr. WINKLER. Oh, yes. I was transferred, but I could not say I was transferred out of my field. My field is internal medicine, and I am currently working in that field in pulmonary disease primarily, but I had been transferred from the Cardiovascular and Renal Division.

Senator KENNEDY. You have been transferred, have you not?

Dr. WINKLER.. Yes.

Senator KENNEDY. Could you tell us from where to where, and the reason you believe you were transferred?

Dr. WINKLER. As I said, my position has been a little bit different. I have been involved in the supervisory role over the past 10 or 12 years, either as a Division Director or Deputy Director, and my most recent position prior to my present one was as the Director of the Division of Renal Drug Products.

I was kept in that Division as a group leader following March 1972, when the new Division was transferred to another physician. I remained in the Division as a group leader, in the pulmonary-allergy group of that division, and more recently, in January of this past year, I was transferred with the pulmonary group into another division, dental and surgical products.

Senator KENNEDY. Do you know why you were transferred?

Dr. WINKLER. I can give you the reasons that were stated at the time, because in March 1972 I asked for the specific reason I was being replaced.

Senator KENNEDY. Who did you ask?

Dr. WINKLER. I asked Dr. Finkle and Dr. Crout, and Dr. Leong, who was there at the time.

Senator KENNEDY. Dr. Crout is what official?

Dr. WINKLER. At that time he was the Deputy Bureau Director.

Senator KENNEDY. What did he tell you?

Dr. WINKLER. The reason primarily was that they wanted to make a management change in the division, and the division had been a major source of complaints from industry.

When I asked for specific examples, there were no specific firms or products or specific instances, but there were general statements regarding difficulty in arranging meetings with the division, difficulty in seeing individuals, things of that nature and discussion on the part of the industry at meetings.

There were other complaints about backlog of supplemental new drug applications being high in the division, and some complaint from within the bureau from other parts.

As I recall, the only one I can remember specifically was that the division was one of the more difficult ones to deal with on the part of the industry implementation group.

Senator KENNEDY. How many were part of the cardiorenal division?

[Drs. Bryant, Winkler, Nestor, Lidd indicated affirmatively.]

Senator KENNEDY. What has happened to that division now?

Dr. WINKLER. In March 1972, the division remained essentially as it was constituted before as far as the type of work.

Senator KENNEDY. Why was the division formed in the first place?

Dr. WINKLER. Why was it formed?

Senator KENNEDY. Yes. Why was this particular team brought together?

Dr. WINKLER. You would have to go back to 1966, I believe, when they first set up divisions within the agency. Prior to that time we did not have divisions or branches set up on the basis of specialty groups, and it was put together as a cardiovascular pulmonary and renal group at that time because of the interrelationship primarily between these fields of medicine.

Senator KENNEDY. To your knowledge was the whole group transferred out of this area of study?

Dr. WINKLER. A good part of the original group has been transferred or realined into other areas.

Senator KENNEDY. Are you being better utilized now, in terms of your background and expertise?

Dr. WINKLER. No, I do not think I am being better utilized. I am still working in the area suitable to my background as far as pulmonary disease and allergy is concerned, but this was part of my work before, but I am also involved with the anesthetic drugs, which is not my field.

Senator KENNEDY. Why would the industry be interested in breaking up this group? Evidently you are doing your job, you are reviewing the scientifically prepared information, the broad data of these other distinguished technicians and scientists.

Dr. WINKLER. Many of the decisions that came out of the group were unpopular decisions with industry. There were many recommendations for nonapproval of new drugs.

Senator KENNEDY. You talk about being unpopular with the American people?

Dr. WINKLER. I say there were unpopular decisions.

Senator KENNEDY. As far as who was concerned?

Dr. WINKLER. As far as the sponsors of the applications in industry.

Senator KENNEDY. They did not like the decisions, and therefore they exercised pressure to see that that group was broken up?

Dr. WINKLER. That is right.

Senator KENNEDY. Dr. Bryant, that was another drug that you worked on, the drug Dilantin?

Dr. BRYANT. Yes.

Senator KENNEDY. Could you tell us a little bit about the FDA official who worked on the matter with the FDA from the other side. Has that ever happened to you?

Dr. BRYANT. Yes. In regard to Dilantin, the former Director of the Office of New Drugs, that office is no longer operative in the Food and

Drug Administration, and who signed the first nonapprovable letter that went out—let me be careful here because I am depending on my memory—who signed an early nonapprovable letter for that drug, and subsequently was employed and is the employee now of the sponsor and represented the sponsor's interest at the advisory committee meeting concerning Dilantin.

Senator KENNEDY. This was a Dr. Hodges, is that right?

Dr. BRYANT. Yes.

Senator KENNEDY. What do you think about that? Did that appear as a conflict of interest to you?

Dr. BRYANT. Well I might say that I think it was mainly an error in judgment on the part of a number of people. Insofar as conflict of interest, that is almost undesignable presently in the Food and Drug Administration, as to whether there actually is such a thing as conflict of interest. I am not being deliberately obscure. I am just trying to say something here that is difficult to communicate. I no longer am sure as to what you mean, what you or anybody else means, when they talk about conflict of interest.

Senator KENNEDY. You want to use the word propriety in terms of this type of arrangement?

Dr. BRYANT. It certainly would be, I think, could be termed improper.

Senator KENNEDY. What about Inderal?

Dr. BRYANT. Well that is a long story.

Senator KENNEDY. Let's try and shorten it up a little bit. Did you approve it or disapprove it?

Dr. BRYANT. Well, first I was not the chief medical officer to review it. I only reviewed a peripheral aspect, but that peripheral aspect of it turned out to be rather exciting, if not, interesting. Dr. Winkler was the official medical officer for review of that; is that not correct?

Dr. WINKLER. Yes.

Senator KENNEDY. Even given this exciting and interesting aspect, did you not disapprove it? Recommend disapproval?

Dr. BRYANT. My recommendations were that it had not been adequately studied, and when it was approved by the division at a division meeting, I indicated the fact that I felt that there was not scientific evidence in favor of it either as being effective or safe, and I went further than that, such as to indicate that there was some suggestive evidence that this drug was not only unsafe, but exceedingly dangerous, for the particular indication that it was being approved for at that time.

You asked me previously of that harassment, or got into the field of that, and this is one of the areas in which I have reason to have the opinion that I was harassed.

Senator KENNEDY. In what way?

Dr. BRYANT. Well I was reprimanded for speaking out in such a fashion, for disagreeing with other medical officers. I assume that this is where—the word escapes me now—the reprimand came from. It was in the form of a private communication with a threat that if I ever did anything like this again, charges would be brought against me.

Senator KENNEDY. Did anything like what again? Recommend disapproval?

Dr. BRYANT. If I spoke out and expressed my scientific opinion in ward rounds as they were called—of course we have no wards and no patients—other meetings and seminars in the Bureau of Drugs.

Senator KENNEDY. Just before we move off this point, there was an advisory committee set up which supported your findings. Is that correct?

Dr. BRYANT. I am told that indirectly. I did not meet with the committee, but I was informed——

Senator KENNEDY. You did not meet with them, but informed——

Dr. BRYANT. No; I was not asked to speak to the advisory committee in regard to Inderal. I had appeared before a previous advisory committee as of about 6 years ago with regard to this.

Senator KENNEDY. But at least it is my information that there was an advisory committee that was established and that supported your scientific findings?

Dr. BRYANT. Let me say that we agreed.

Senator KENNEDY. I see. You had a meeting with Dr. Apter—wasn't Dr. Apter on the advisory committee?

Dr. BRYANT. Yes. Dr. Apter also served as a consultant on Hexabendene, and that was the meeting that I presume you were referring to?

Senator KENNEDY. Did you call to the attention of Dr. Apter the misrepresentation of the advisory committee.

Dr. BRYANT. Yes, that is a separate issue. I knew that Dr. Apter was a member of the advisory committee and at one of our division meetings, that is the Division of Cardiorenal Drug Products, information was presented to indicate that the position of the advisory committee had been misrepresented as a basis for approval of Inderal for the treatment of angina pectoris.

Senator KENNEDY. Now Dilantin and Inderal are both drugs which are currently on the market for some uses, and your review, as I understand it, was geared around expansion of those uses?

Dr. BRYANT. That is correct.

Senator KENNEDY. Were they widely used in the medical profession at that time for unapproved uses?

Dr. BRYANT. I have reason to think that they were, and my reason for it is without documentation whatsoever, but a fantastic amount of testimonial evidence. In other words, doctors say, "why it is used everywhere," that is, Inderal, for the treatment of angina pectoris, and insofar as documenting that goes, I know of no documentation other than hearsay.

Senator KENNEDY. If that were true, it would probably bring considerable pressure for approval on the FDA?

Dr. BRYANT. Yes. I was certainly exposed to the most intense type of pressures for the stand that I had advocated on the non-approval of Inderal in the treatment of angina pectoris. This went on for years, and it never seems to end. In December 31, I think, 1969——

Dr. NESTOR. That is correct, not 31, but December.

Dr. BRYANT. This represents a rather unique experience in which there is cooperation between industry and a part of academic medicine, and I think part of academic medicine is responsible, although I looked backward with pride on the 25 or more years that I served on medical faculties.

Senator KENNEDY. Dr. Kennedy, we mentioned earlier some of the experiences you had in the overturning of some of the recommendations you had made to disapprove specific drugs. Could you share with us your experience on a particular drug called Cylert?

Dr. KENNEDY. Yes.

Senator KENNEDY. Just in general terms, tell us why you recommended nonapproval?

Dr. KENNEDY. I have to say two things first to set the scene for the way that things went. First of all, at this particular time in the Division we were required to have certain-check in points, so to speak, where the reviewing team would meet and report our findings to the Division Director. Also on all new drugs we were required to have an outside consultant to review the application with us before the drug could be approved.

I received Cylert in December, I believe it was, it was submitted in November, but I did not get it 24 days later, the reviewing team which consisted of a chemist, Mrs. D'Acosta, who is a pharmacologist, and myself, met in February. We all were in agreement there was insufficient data to approve it at that time. I am not going to go into the pharmacology deficiencies because that is Mrs. D'Acosta's expertise. There were chemistry deficiences which had been present since 1969. This was a period of time when the agency was trying to establish guidelines for drugs to be used in children. And when I presented my review, my findings of the clinical data plus the other deficiencies at that time, the Division Director requested that I obtain a group of consultants to advise the FDA on guidelines for drugs to be used in children. This was one issue. An independent review of the drug, of the data, was done by Dr. Allen K. Done, whom I have mentioned before, who was Special Assistant to the Director on Pediatric Pharmacology.

Dr. Done independently, with his review of the data, agreed with my recommendations which had been set forth in a summary of nonapproval in April.

Following this, I believe it was in May, I met with Dr. Gerald Solomons who was coming in as the chairman of the task force on guidelines, and I had previously presented him with a copy of the protocol. He had his independent comments to make on that.

At this meeting in May with Dr. Solomons, Dr. Done, myself, Mrs. D'Acosta, I presented a summary of my review of the data. I did not present my conclusion until Dr. Solomons was allowed to give his comments, and in essence he agreed with all of us that there was insufficient information on which to base approvability of this drug.

Subsequent to this, or actually briefly before that, Dr. Gardner had agreed we should go ahead and issue a nonapprovable letter to the firm, based on pharmacology and chemistry deficiencies, rather than waiting for the clinical discussions which obviously had to come at a later date. This was agreed to in writing and we were prepared to send the letter. Mrs. D'Acosta and I, who had discussed the pharmacology deficiencies, we had both drafted our positions of the letter, plus the chemist had drafted his, we were informed by the chief pharmacologist that she could not agree to the issuance of the nonapprovable letter which included the pharmacology deficiencies. Be-

cause the team was concerned, we scheduled a meeting with the Division Director to clarify the situation and see where we stood.

The meeting was scheduled. The meeting was canceled without any invitation to the members of the reviewing team or without advising the reviewing team, the Division Director met with representatives of the drug firm and I was subsequently——

Senator KENNEDY. Were you present?

Dr. KENNEDY. No; I was not present. I was not informed. I found out the following day, a Food and Drug officer informed me that the Division Director had told him that he had informed the drug firm that there were no serious problems with the drug, that it would be approvable subsequent to that. I will not bore you with all the details of phone conversations; but representatives of the drug firm did indeed confirm that they had received this information, that there were no serious problems with the drug.

Senator KENNEDY. As I understand it, you made a recommendation, and then you had a consultant who worked with you who concurred in that recommendation?

Dr. KENNEDY. Had someone from the FDA itself who was a special assistant on pediatric pharmacology and who is a well known pediatrician. I also had an outside FDA consultant who is very experienced in this area.

Senator KENNEDY. They agreed with you?

Dr. KENNEDY. That is correct.

Senator KENNEDY. You had an advisory committee?

Dr. KENNEDY. Well that comes later.

Senator KENNEDY. I see.

Dr. KENNEDY. We met, first of all, the reviewers met with the sponsor to inform them of our findings. Present at that meeting was the reviewing team, Dr. Done, and members from the drug——

Senator KENNEDY. We don't necessarily have to have that.

Dr. KENNEDY. We presented our findings. The firm had told me they were trying to get a separate meeting to our meeting with the Division Director. However, the Division Director was to come in at the end of this meeting. He was not present at this meeting. Following the meeting with the suggestion of Dr. Done, the firm was presented with a copy of the draft letter, which indicated nonapprovability. We had already discussed the contents.

They were informed it was a draft. And the next thing I knew, I was being called, along with Dr. Done and members of the reviewing team, to brief other people in the agency, and I was called to brief Dr. Simmons, who then was Bureau Director and Dr. Finkel, who then I believe was Director of——

Senator KENNEDY. What were the conclusions of the advisory committee?

Dr. KENNEDY. The conclusions of the advisory committee which came after meetings with the Commissioner, with Dr. Simmons, Dr. Finkel, the final conclusion—I am leaving a large part of the information of course is going to be missing—but they agreed with me.

Senator KENNEDY. They agreed with you?

Dr. KENNEDY. There were three members who independently reviewed the data, plus Dr. Apter was called in for her opinions on the statistical review.

Senator KENNEDY. So your representation, the consultants, the in-house specialists, and the advisory committee all agreed. Then what happened?

Dr. KENNEDY. After this, after some discussion, a letter of nonapproval did issue. A rebuttal came in. I was informed that I was not to review this data. Furthermore, I was not to have any more contact with the consultants. This was by the Division Director.

Senator KENNEDY. Did they give you any reason for that?

Dr. KENNEDY. I was just told if I communicated with anyone else outside the agency, I did so against advice.

Following this, the Division Director reviewed data on his own, I had a meeting with him, with Dr. Crout, well, with Dr. Done, Dr. Crout, Dr. Gardner, and another member at that level. I was informed that the reviews that were done by myself, by the consultants, were not done dispassionately or competently. I was told that I was to write no more memorandums for the file. I was told a new ad hoc committee woud be obtained for which I would not have really any input. All the contacts would be from the Division Director and the Deputy Director, and they would have no contacts with the other group of consultants.

Senator KENNEDY. Then what happened? There is a lot, I am sure, but I am trying to direct your attention to the task force report or the second advisory committee.

Dr. KENNEDY. I was not involved in the second advisory committee.

Senator KENNEDY. You know what they concluded?

Dr. KENNEDY. I know they concluded there was insufficient data to approve the drug.

Senator KENNEDY. That is what had been your first observation?

Dr. KENNEDY. That is correct.

Senator KENNEDY. You, the consultants; the in-house assistants, and the first advisory committee reached a decision, then you were told to stay away from any more communications. Then, as I understand it, there was the second advisory committee that upheld and substantiated your initial findings, is that correct?

Dr. KENNEDY. That is correct. But prior to the meeting of the second advisory committee, I was removed from the Division. I was detailed just shortly before the second meeting—second advisory committee meeting was to occur.

Senator KENNEDY. Was that in response to your request?

Dr. KENNEDY. No. It was over much protest. I was called late one evening by Dr. George Leong who asked me if I would agree to help him out in the Division of Dental Surgical Drug Products to review soft contact lenses, because they had——

Senator KENNEDY. Review what?

Dr. KENNEDY. Review soft contact lenses because they had a backlog in that Division. And I as a psychiatrist could not understand why I was being sent to review soft contact lenses.

I tried to find out from the Division Director who told me I would have to talk to Dr. Crout. I finally got a memo saying it was indeed because of a backlog. I remained in that Division for the period of the detail. I requested a return to my own Division.

When I returned, I found that I no longer would be reviewing the drugs in my area, but that I would be again helping with the backlog of drugs which were used for nausia, vomiting, and migraine headaches.

Senator KENNEDY. How many psychiatrists were in the Division when you were there?

Dr. KENNEDY. When I was there, there were three, plus the Division Director, and also later on a psychiatrist neurologist.

Senator KENNEDY. How many are there now?

Dr. KENNEDY. Well as far as I know, there is one psychiatrist who is still reviewing drug data. They have brought in three psychologists. Shortly after my removal, they were advertising for psychiatrists, so they may have some more by now. I don't know.

Senator KENNEDY. It would appear from what we have heard that the Cardio-pulmonary-renal Division has been deciminated, apparently because of industry pressure, and now we have had the effective disbandment of your division. Let me ask you this: did this happen to you with any other drug?

Dr. KENNEDY. You mean were there other advisory groups?

Senator KENNEDY. Did you have a similar experience with Tofranil?

Dr. KENNEDY. That was one, I mentioned when I gave the reasons or felt that data were insufficient to approve it at that time, it was just simply removed from me.

Senator KENNEDY. That was ultimately approved?

Dr. KENNEDY. That was approved.

Senator KENNEDY. Are there problems showing up now?

Dr. KENNEDY. As I understand, the British medical journals are beginning to see problems with the drug. I may say this drug is approved for another indication. Our concerns were the use of the drug in children because it would be used over a long period of time, in spite of the fact of the limitations which were to be employed for a short period of time for bed wetting. We note from a review of data contained in the record that it was often used for as long as a year. We were concerned about the effects, possible effects on growth, infant functions, et cetera.

Senator KENNEDY. We have some correspondence that has been unsolicited from doctors related to Tofranil, where they mention the problems they have faced as well on this. They have signed the letters and are practicing physicians and we will just make that a part of the record.

[The letters referred to may be found in the files of the subcommittee.]

Senator KENNEDY. Can you confirm that there are still unsolicited samples being sent through the mail for Tofranil?

Dr. KENNEDY. I do not know about this.

Senator KENNEDY. We have a staff member, a physician, who received three samples last week unsolicited. Your conclusion from the work in the FDA is: is it easy or hard to disapprove new drugs?

Dr. KENNEDY. For me it was extremely hard.

Senator KENNEDY. To do what?

Dr. KENNEDY. To disapprove. I had to justify my position many, many times, at many levels, through administrative echelons.

Senator KENNEDY. Mrs. D'Acosta, you worked with Dr. Kennedy?

Mrs. D'ACOSTA. Yes, I did.

Senator KENNEDY. You were opposed to approving the drug as well?

Mrs. D'ACOSTA. Yes.

Senator KENNEDY. Why did you conclude it should be disapproved?

Mrs. D'ACOSTA. I was opposed to approving the drug because the clinical indications for the drug was for long term usage. I had reviewed that animal data that was available, and I found no evidence to support any long term use of the drug, specifically in the pediatric category.

I might give you a little background as to procedures for the pharmacologist's review, as you discussed earlier with the medical officers.

The procedure is that the reviewing pharmacologist evaluates the application and submits the review, the rough draft of the review to the senior pharmacologist, who then is in agreement with the conclusions of the reviewing pharmacologist, initials the rough draft and then sends it forward for typing and processing.

I might take one step back to point out that at the time I was given the NDA (new drug application) for review, Dr. Edward Tokas was the senior pharmacologist. He received my review and recommendations regarding the drug and evaluation of the data that was submitted with the NDA. He signed off on my review. There was total accord with the evaluation I had made, based on the data submitted, and it was put forward as an official pharmacologist review.

There came a point in time that Dr. Tokas was made chief of the Drug Abuse staff, which was a part or unit contained in the Neuropharmalogical Division.

Subsequent to that, Dr. Glocklin became chief pharmacologist. At that point Dr. Kennedy mentioned that the chief pharmacologist did not in fact concur with the evaluation that I had made of the application, and I gave you that background information to delineate who was chief pharmacologist and at what time and period.

Senator KENNEDY. I understand you agree with Dr. Kennedy's testimony?

Mrs. D'ACOSTA. I agree entirely.

Senator KENNEDY. You were on the first advisory panel?

Mrs. D'ACOSTA. I was not on the first advisory panel, but I was involved with the preparation of the material that was submitted to them. In fact I was invited by the panel to join them in their discussions and deliberations and acted as a resource person during their conferences.

Senator KENNEDY. Were you ever cut off from access to the files?

Mrs. D'ACOSTA. Yes, I can't remember the date, but there was a point in time when a memo issued from the Division Director's office, who was then Dr. Elmer Gardner, and it was directed to all professional staff people. The substance of that memo was that the Division file would not be available to the professional personnel unless a request was made through the consumer safety officer, who would in turn relate this to—I am not sure where the point of authority went at that point, I am not sure whether or not the consumer safety officer had to consult with Dr. Gardner or someone else at the Division level, as to whether or not the professional would have access to the file. If permission were granted, the professional was brought the file by the consumer safety officer, and this is the way we were able to gain access to the files.

Prior to that, however, I might say, professionals had freedom to consult the files at any point in time of day, and I also might add this was a very necessary process for us to—in our reviewing to consult files to determine whether or not there were other applications, other drugs, that would have material pertinent to the particular application that you were reviewing.

Senator KENNEDY. Now as I gather, you were effectively taken off the case about the same time Dr. Kennedy was?

Mrs. D'ACOSTA. Well, this is in essence correct. I might add, however, that the record will show that I made a request to be transferred to the Drug Abuse Unit, then headed by Dr. Tokas, my former supervisor. There are circumstances that I will not go into now that precipitated this request.

Senator KENNEDY. You also agreed with Dr. Kennedy on Tofranil, did you not?

Mrs. D'ACOSTA. I did.

Senator KENNEDY. Dr. Lidd, you previously commented that your review of Cylert resulted in your recommendation for disapproval being overturned. Can you tell us why you recommended disapproval?

Dr. LIDD. Well, of the twin factors of safety and efficacy, the point of reference was with respect to efficacy. I felt that there was not sufficient substantial evidence based on well controlled studies to substantiate the claim made.

Senator KENNEDY. Did you find there is more pressure in your experience for approving the drug than disapproving it?

Dr. LIDD. The Serc episode occurred in the late 1960's. I would say fortunately, maybe because the material I have handled, I had very little pressure I think maybe because the problems I had were rather clear cut.

Senator KENNEDY. Were you transferred out of the Cardio pulmonary-renal Division?

Dr. LIDD. In the early part of this year I was transferred into the anti-inflammatory group of the Division of Radiopharmaceuticals and Oncology.

Senator KENNEDY. Are there any full time cardiologists in the Cardiac Division now that you know of?

Dr. LIDD. I do not know who is there right now. I am no longer in that division.

Senator KENNEDY. Why would you be transferred out of the area of your maximum expertise?

Dr. LIDD. Well, at the time the Cardiopulmonary Division was modified, my area of expertise would have put me in the same division presently that Dr. Winkler is in. I was not assigned to that division. Instead I was assigned to the other division. I was never given an answer—pardon me—I was never given any information as to why I was assigned to the particular division I am in now.

Senator KENNEDY. Did you ask about it?

Dr. LIDD. No, I did not.

Senator KENNEDY. You are outside your area of expertise, are you not?

Dr. LIDD. For the most part. My background is in pulmonary disease, allergy, and immunology. Fortunately immunology is in almost every

field. So there is some immunology in the field I am in. My primary area would be elsewhere though.

Senator KENNEDY. Did you work on any drugs where tumors showed up in animals after human testing had been done?

Dr. LIDD. Yes, sir.

Senator KENNEDY. How many?

Dr. LIDD. Either solely or in conjunction with others, I believe three.

Senator KENNEDY. Does that indicate incomplete animal testing prior to human testing?

Dr. LIDD. If one looks at the aspect of the potential of any given drug to cause tumor formation, one would have to say that one would need long-term animal studies to elucidate whether or not that potential exists for a given drug. There are so far no acceptable short term methods of predicting that aspect, although there are some controversies in terms of the role of the studies. With this in mind, one would, in order to rule out tumor potential, have to have long-term animal studies.

Senator KENNEDY. Dr. Gerda, have you been transferred by FDA?

Dr. GERDA. I was formerly in the Division of Dental and Surgical Products and was transferred out this past year during the reorganization which just took place recently.

Senator KENNEDY. From where to where?

Dr. GERDA. I was transferred to the Division of Radiopharmaceuticals and Oncology.

Senator KENNEDY. You are a surgeon, are you not?

Dr. GERDA. Yes.

Senator KENNEDY. Do you know why you were transferred?

Dr. GERDA. No. I was not informed or consulted regarding this transfer. The notice I received, as I told Mr. Sheridan, was the plan of reorganization in which all medical officers were listed in their new divisions.

Senator KENNEDY. What sort of work are you doing now?

Dr. GERDA. I am working with the radiopaque media, radio contrast agents. I might say this is not a new area for me. I had worked with these agents previously because these drugs had been assigned to the Division of Surgical and Dental Products previously. But under the reorganization, it was felt, I assume, that it was more logical to include them under radiopharmaceuticals, since the radio contract media used by radiologists mainly—and of course radio pharmaceuticals—are primarily in that area of specialization. So the transfer was logical in some ways although I was not consulted, as I said, or asked whether I would like to take on this class of drugs.

Senator KENNEDY. Did you inquire why you were being transferred?

Dr. GERDA. No; I did not. At the time the circumstances were such that I felt there would be no use in doing that.

Senator KENNEDY. Now you are working in the radiopaque material?

Dr. GERDA. Yes.

Senator KENNEDY. Would you tell us about your experience with having your recommendations for disapproval being questioned at high levels?

Dr. GERDA. Well I have not had real direct pressure brought on me to change any recommendation that I have made, although the kind of

pressure that I have felt has been more in a general area of review, of review provinces. By that I mean ever since I have been here, I have been concerned about the basic scientific data and application, and I would like to go through the control data and particularly the stability studies, and very, very closely the pharmacology data because I have always felt that a medical officer cannot make a decision on clinical studies unless he is very or pretty much aware of the animal studies that had been done on an application.

I have always felt that there should be some freedom or there should be complete freedom on the part of the medical officer to analyze the animal data and criticize it and make recommendations on these data. So the kind of pressure that I have felt has been this controversial aspect of whether a medical officer should actually get himself involved in reviewing controls in animal data. It reached the point at one time where the supervisory staff of our dental and surgical division called a meeting in which I was the only medical officer present and at that time a decision was reached that the medical officer should evaluate animal data and control data, but should not put his findings or his recommendations in writing in the actual review.

Now, the reason for this, I have never really known, but this was just the Division policy that was reached. I understand it was debated up in the higher management areas, although I was not present at these meetings, and I do not know what the Bureau's general policies on that is yet. So in listening to my colleagues telling about their experiences dealing with clinical animal work, I am in general agreement, I think these areas of animal studies—in particular, the chronic animal studies—are very important. There is no way of telling whether a drug will be carcinogenic on suspicion or on analogies. The only way is to require animal studies.

Senator KENNEDY. Did you do some work on Discase?

Dr. GERDA. Yes.

Senator KENNEDY. And what was your recommendation? Did you recommend approval?

Dr. GERDA. Originally, I did not recommend approval on that. That is a long story.

Senator KENNEDY. Very briefly, let me ask you some specific questions on Discase. Were there any outside groups convened to review the data?

Dr. GERDA. Yes.

Senator KENNEDY. And those outside groups supported your finding?

Dr. GERDA. Yes.

Senator KENNEDY. Then, was it referred to another group?

Dr. GERDA. Originally, we had an ad hoc committee of distinguished neurosurgeons and orthopedic surgeons to review this drug. This drug is an enzyme preparation which is injected into a ruptured or extruded disc, in the treatment of the back syndrome. There are two groups in the country that would use this type of drug. That would be neurosurgeons, who do surgery for these conditions, and also the orthopedic surgeons.

So we convened an ad hoc committee to review these data, and they generally agreed with my findings, and in addition expanded their recommendations on the basis of their expertise.

Senator KENNEDY. Then another advisory group was convened, was it not?

Dr. GERDA. Well, not really. About this time for some reason, I am not aware of why, the ad hoc committees were discontinued. I believe our ad hoc committee on Discase was the last ad hoc committee in the Bureau; and shortly after they made the recommendations on this drug, the committee was disbanded.

Senator KENNEDY. Was your involvement terminated?

Dr. GERDA. Not at that time.

Senator KENNEDY. At any time?

Dr. GERDA. Yes. It terminated actually when the reorganization took place—I am sorry, not quite then. It was about a year prior to the reorganization, when Dr. Clark was made Division Director, following Dr. Ridgebee's resignation. I won't go into the details.

Senator KENNEDY. It seems you did the original work on the drug, and had an advisory committee review your work, which supported it, and while it was still in the process of being considered your participation was terminated?

Dr. GERDA. Here again it was not that abrupt. I was never actually consulted or told that I would no longer be reviewing the drug. But when Dr. Clark came in, there was a key meeting between the industry representatives of this drug and Dr. Crout, at which time——

Senator KENNEDY. Were you present?

Dr. GERDA. Yes. At which time various details of the deficiencies of the clinical studies and other aspects of the NDA were discussed. Following this key meeting is the point at which I stopped having a direct contact with the drug, although I did review such things as adverse reactions on the drug subsequently and a few other minor details.

Senator KENNEDY. At that meeting with the industry, did you express your reservations?

Dr. GERDA. Yes.

Senator KENNEDY. So you made your findings, supported by the advisory committee, you have a second review committee, and then you have a key meeting with industry people and Dr. Crout, and you expressed your concerns and reservations, and then shortly after that your work with that review terminated. I think that is the sequence of events.

Dr. GERDA. It was not quite that abrupt.

Senator KENNEDY. OK.

Dr. GERDA. As I say, this was a complicated story. Shortly after the first ad hoc committee was disbanded, this drug was then presented to the new advisory committee, with the surgical and dental advisory committee, which was part of the general advisory committee system that was initiated in the Bureau. From then on, the surgical advisory committee really handled the drug.

At the first meeting, I presented the general picture of this drug, and the decision at that time was to form a subcommittee of the surgical advisory committee, and that subcommittee really went into the data. They were the ones who subsequently decided what was to be done with the drug. I do not know what the current status is, because I was transferred out of the Division. As I was telling Mr. Sheridan, the subcommittee has been really carrying the ball on this drug since that time.

Senator KENNEDY. The only thing is, Doctor, it seems you were very much involved in the process, then you expressed your views, and were transferred out of the Division. You were not given any explanation for the transfer. We will let the record stand as it is.

Dr. Campbell, I believe hydergine was one of the drugs you were working on.

Dr. CAMPBELL. I have not actually had recommendations overruled. The situation with hydergine was, on two occasions——

Senator KENNEDY. Bring the microphone a little closer.

Dr. CAMPBELL. With two different submissions from the firm on that particular drug, I turned both submissions down because of the method of study, the question as to whether the people who are in the studies actually had the diagnosis and the problems for which the drug was to be used.

In fact, I turned the drug down on all aspects, clinical material, the question of safety, and the final statistical analysis in which the conclusions were certainly questionable. After I turned down the second submission, the firm went to the administrative echelon to ask questions, and I found out about this after this, when I was called up, by myself, to the Director's office, and she questioned me as to why I turned the drug down, and I gave her my reasons.

Shortly, thereafter, I went on vacation. When I returned, I found that the drug had been removed from my office and was submitted to the statistician for further review, which I had decided not to do since the clinical review really did not warrant approval.

I did not think it was much point in wasting the statistician's time. One week after I came back from vacation, I was called into Dr. Gardner's office, who was Division director at that time, and I was told in no uncertain terms that I was to give the drug application to Dr. Stovall, who was Dr. Gardner's Deputy Director, and he would then either review it or assign it to another medical officer to review. I protested this because the drug application was in the behavioral altering systems in the elderly, and since I was a psychiatrist, and Dr. Stovall or any other physician in the agency to whom the drug could have been assigned was not a psychiatrist, both of the other psychiatrists were already very busy with all sorts of drugs, and after that within 6 months Dr. Stovall reviewed the material that I did and came to a completely different conclusion. I found this out only sort of inadvertently because I was no longer involved with the drug.

In August of 1972 Dr. Gardner asked me to present the drug to the advisory group on neuropsycopharmacology. I went back to review the file in order to see what sort of things had happened with this drug subsequent to my being removed from it. What I found in the file led me to submit to Dr. Gardner a question and memorandum, whether I could in fact submit to the advisory committee, since it was my belief that the advisory committee could be well served only if I were to submit to them all the data and all the administrative decisions and all activity of the FDA. I asked that instead the drug be given to my task force on psychoactive drugs in the elderly.

At that point I can only say that from that point on it was a downhill course. My memorandum in question was never acknowledged by Dr. Gardner. I started to find a lot of strange things happening to me, and finally after a couple of months I was advised that I could get one

of my consultants to look at the material, he did come in to look at it. He agreed almost entirely with my recommendations, but more importantly when I reviewed it with my consultant, I found a memorandum which had been directed to file, and Dr. Crout accusing me of uncooperativeness, incompetency, unreasonableness. I had never been informed of that memorandum. It had never been discussed with me, and at that point of course the thing blew apart.

Senator KENNEDY. Did you receive a letter of reprimand.

Dr. CAMPBELL. I received a memorandum of reprimand at this time. Subsequently I had all my—every single bit of my work removed from me with a notice to the management person that I was not to be informed of the——

Senator KENNEDY. Speak into that mike.

Dr. CAMPBELL. I submitted a personal grievance on the fact that I had had my entire work removed from me, not only this one drug, but all the other work. I had actually been working on antidepressants and all psycoactive drugs used in the elderly. Everything was removed from me without my having been informed, with the directive to management personnel that I was not to be informed.

Senator KENNEDY. That reprimand was withdrawn later on?

Dr. CAMPBELL. The letter of reprimand came some months later. When I continued to question, and through former channels continued to in effect defend my position, that on no previous occasion or no situation had I ever been called incompetent, inadequate or unreasonable——

Senator KENNEDY. Did you find that after you had rejected some drugs, the nature of your job began to change or you were transferred?

Dr. CAMPBELL. Yes. The nature of my job—more importantly, however, the situation became such that when any questions arose as to how to continue handling the drug, that the Division Director was in fact never available for questions. Memorandum of questions were never acknowledged or answered. Meetings were held with drug firms in which all the other members of the reviewing team, in some instances were not invited. I was not invited. In other instances the Division Director met with members of the drug firm with no member of the reviewing team available, and in a good number of instances no member of the reviewing team was advised of what actually happened during those meetings.

Senator KENNEDY. These are meetings with the companies?

Dr. CAMPBELL. These are meetings with the drug company agents, yes.

Senator KENNEDY. At some point you were transferred?

Dr. CAMPBELL. I was transferred, I can give you the exact date because it is burned into my memory——

Senator KENNEDY. Speak right up.

Dr. CAMPBELL. On July 23, 1973, I was requested to report to the Methadone Monitoring Unit by Dr. George Leong. On the same day I got a letter from Dr. Elmer Gardner saying the letter of reprimand which he had originally submitted in my case would stand in my file for 2 years.

You are quite correct. That letter of reprimand was subsequently rescinded when I brought a lawyer into it, and 41 pieces of documentation showed that there was no way he could support a letter of reprimand.

Senator KENNEDY. Were the reasons for the transfer made known to you?

Dr. CAMPBELL. The reason given to me was that psychiatric expertise was absolutely vital in the methadone monitoring unit, and I must emphasize here that in the year that I have served in that unit I have used my psychiatric expertise on no single occasion.

Senator KENNEDY. No single occasion?

Dr. CAMPBELL. No single occasion.

Senator KENNEDY. Had there been prior to your going there some psychiatrists that had been actually transferred out of there?

Dr. CAMPBELL. Out of methadone monitoring?

Senator KENNEDY. Out of where you came from?

Dr. CAMPBELL. Dr. Kennedy had been detailed to review soft contact lenses, and about the same time I was transferred out of the Division of Neuropharmacology had been detailed in the Division of Neuropharmocology to review nausea, vomiting, and migraine drugs.

Senator KENNEDY. I want to recognize the presence of our ranking Republican member, Senator Javits, who is also an active member of our Health subcommittee.

Senator JAVITS. Thank you, Mr. Chairman. Ladies and gentlemen, I have just been advised of the very, very serious charges which are being made here on the sworn testimony by professionals, who are well-educated and respected professionals, and I am very deeply shocked and troubled by it.

I am the ranking minority member of the Labor and Public Welfare Committee. We have a ranking minority member on this subcommittee, Senator Schweiker of Pennsylvania. I regret very much that because of his marking up of an appropriations bill, and my concern with a new budget committee, which is having its hearings this morning, that we have not heard your sworn testimony personally.

But I wish to assure you that whatever you have said has not fallen on deaf ears at all. I work very closely with Senator Kennedy, the chairman of the subcommittee, and with Senator Williams, who is the chairman of the full committee, and we will give the most considered and intensive attention to the points that you have made, either myself or through the ranking and other minority members of the subcommittee.

I came specially from the other hearing, just to assure you, in fairness to you, of that fact, and that I am deeply impressed with what Mr. Cutler, our minority counsel, has advised me about the gravity of the charges made and also about the character, high character of the people that have made them.

Though I have not been here, nor has Senator Schweiker or the other members of the minority, I want to assure you that it will be taken with the greatest seriousness and that every word you have said will be carefully considered, and as far as we are concerned, followed up in as vigorous a way as Senator Kennedy would himself.

Senator KENNEDY. Thank you very much.

Dr. Appleton, could you describe the pressures you have received from superiors after submitting unfavorable reviews?

Dr. APPLETON. I think my situation in the agency is now stabilized. This kind of situation had been a way of life before my transfer to my current assignment. I would just say that there have been occasions

where I have made findings that did not meet with the approval of my supervisor and that the applications were then removed from my purview.

Senator KENNEDY. Why do you think they were removed after you disapproved them?

Dr. APPLETON. Well, in my studied opinion, and as I saw the applications before me, the data in the application did not meet the requirements of the regulations with respect to chemical purity and analytical methodology, and the way that these questions were resolved was to simply remove these applications from my continued review.

One situation comes to mind, and this is some years back when my review found that the application did not meet even the minimum requirements of the U.S. Pharmacopeia. I think the applicant understood it, I think the agency understood it, I certainly understood it, yet this application was subsequently approved. I tried to use all the machinery available to me including a provision in the law which would try to bring such attention to the U.S. Pharmacopeia, but my efforts died aborning within the agency. So it was this kind of difficulty that I had had, in simply trying to do a job, to do it to the best of my ability.

Senator KENNEDY. Did it happen to you more than once that you made recommendations and then found that you were transferred out of consideration?

Dr. APPLETON. Well, the circumstances surrounding that——

Senator KENNEDY. Just yes or no, rather than getting into the details. We do have to move the hearing. That did happen to you?

Dr. APPLETON. Yes, that happened in my previous assignment, yes.

Senator KENNEDY. And you have been transferred from one division to another?

Dr. APPLETON. Yes; I have.

Senator KENNEDY. Can you tell us what the occasions were?

Dr. APPLETON. Well, Mr. Chairman, this goes back 3 or 4 years. I made a complaint, a formal complaint, against a supervisor for what I considered to be interference with my professional work, of the kind that I was describing.

Senator KENNEDY. Would you tell us about that just briefly?

Dr. APPLETON. It involved essentially making statements to sponsors and to applicants about the way I was reviewing applications and incorporating, at least in one instance, at least, in a memorandum for the record, which I considered in my non-legal mind as libelous or slanderous—I let that lie fallow for a number of years, and I did not think anything of it. I was continuously harassed in the way I was trying to do my work.

As a result of that, I brought a formal complaint and the reply to that complaint was the attempt to effect my discharge. After extended hearing on both the cases. there was a trade-off. The charges against me were dismissed, and before the actual dismissal of the charges, I was transferred out, with my approval, out of the Division.

[The following information was subsequently supplied for the record:]

During the hearings in 1970 of the agency's case against me (prior to my actual transfer in early 1971) I was offered a transfer from the Division of Metabolism and Endocrine Drug Products, then headed by Marion J. Finkel, M.D., to the library of the Bureau of Drugs by George F. Leong, Ph D. who then served in the

Office of Scientific Evaluation. Dr. Leong offered me this position, whose duties he did not define but which I could easily discern as being totally meaningless, on the basis that I "like to use the library." I rejected the offer on the grounds that I did not want to do nondescript work (I did not want to become a "paper clip") and that such transfer could prejudice the outcome of my case then in progress. I heard nothing further about a transfer until early 1971 when I was offered and accepted my current assignment.

Senator KENNEDY. Do I understand that one of the reasons that you filed the complaint was because your superiors were meeting with drug company officials?

Dr. APPLETON. My immediate supervisor at that time. I would say, was going behind my back.

Senator KENNEDY. How was he going behind your back?

Dr. APPLETON. He would communicate my findings to the sponsor without telling me about it.

Senator KENNEDY. I would say that is going behind your back.

Dr. APPLETON. He never consulted me about some of the things.

Senator KENNEDY. Do you know that for a fact?

Dr. APPLETON. Well, I have some evidence to that, some altered reviews. I have had occasion where my reviews were altered unbeknownst to me, which I found only by inadvertence much later than the actual occurrence. It was generally an unpleasant experience in trying to follow the dictates of the regulations under which I was supposed to work.

Again in line with some of my medical colleagues, the burden is on the reviewer, when he expresses disapproval, when he finds nothing wrong—I have never been questioned, it is only when one makes adverse findings of a chemical nature.

Senator KENNEDY. What department are you in now?

Dr. APPLETON. I am in the Division of Neuropharmacological Drug Products.

Senator KENNEDY. Do you get a chance to review drugs now?

Dr. APPLETON. Yes. I am doing the same kind of work I did before.

Senator KENNEDY. Dr. Knox, did you have similar experiences?

Dr. KNOX. I remember one case where I recommended disapproval of the drug, and I found the drug was removed from my purview and given to another medical officer, who promptly recommended approval.

Senator KENNEDY. Is that an amphetamine?

Dr. KNOX. It was an amphetamine-like drug, not an amphetamine; a similar drug. I asked why he had not contacted me. He said I might prejudice him, that it was better for him to operate without any preconceived notions of mine. However, he already knew, I am sure, what my notions were because I had made them fairly public.

I later complained that when I did finally get a copy of the review much later, that he did not have anything in his review specifically about the amount of weight loss. This was a drug for obesity, and I felt his was a glaring requirement that had been overlooked. I believe subsequently the review was altered to include something about weight loss.

Senator KENNEDY. Were the files ever altered or changed?

Dr. KNOX. I believe so.

Senator KENNEDY. Do you know whether any of the material that you put in the memorandum was either altered or taken out or reviewed?

Dr. KNOX. The only thing I recall was that the other medical officer's review, which did not have anything about weight loss in it, when I looked at the file some months later, it had a sentence or two added at the bottom of the page without indication as to the fact that it was a later addition.

So when you looked at it, it looked like the original——

Senator KENNEDY. It looked like part of the original file?

Dr. KNOX. That is right. We normally write a separate amendment, if we are going to alter our opinion, wish to alter anything about medical officer review. In this case it was inserted at the bottom of the page and appeared it had been done at the same time as the original review.

Senator KENNEDY. Do you think it is important for the reviewing officer to go over the raw data?

Dr. KNOX. Very important. I think this is essential.

Senator KENNEDY. Have you ever had any experiences where the review turned up a serious deficiency that the summary might not have caught?

Dr. KNOX. I am not clear as to the question.

Senator KENNEDY. I mean, when the summary fails to take into consideration some of the facts which you reviewed by the raw data.

Dr. KNOX. You mean the sponsor's summary?

Senator KENNEDY. Yes.

Dr. KNOX. Yes, I find the sponsor's summary is not always what I would like, that it does not contain an analysis that I would agree with.

Senator KENNEDY. How about the rest of the panel? Do you agree with that as well, the importance of raw data?

Dr. BRYANT. Yes.

Senator KENNEDY. Would the record show who agrees with that?

[Show of hands.]

Senator KENNEDY. What impressions did you gather, Dr. Knox, of the influences of the drug industry on these decisions in altering or changing the decisions?

Dr. KNOX. One reason I was told that the drug was taken out of my office was that the drug firm had objected, that I was biased. I replied by saying that it seemed to me to be putting in the drug firm's hands the decision as to who would review the drug.

We went along that way. There was no change.

Senator KENNEDY. Have you been transferred?

Dr. KNOX. About 3 years ago I was transferred from the Division of Bureau of Pharmacology and Oncology to Radiopharmaceuticals.

Senator KENNEDY. And you feel you are being properly utilized now?

Dr. KNOX. My specialty is internal medicine, and when I came to the Division I was assigned to hematologic drugs. It does not appear in the title, though. Subsequently I was transferred out of the Division, however, and now I have been reassigned to Radiopharmaceuticals.

Senator KENNEDY. Do you think the review process ought to be more open to the public?

Dr. KNOX. That is a difficult question. I realize that there must be some trade secrets, but in some instances I feel that they can be more open.

Senator KENNEDY. Okay. Dr. Ciarla, as you are aware, this subcommittee has been interested in the area of adverse drug reaction. We have had different testimony before the subcommittee regarding this, with reports on various figures. One of the things we are interested in is the development of information on how much drug reaction there has been. You wrote a memo on July 25 raising questions about what you consider to be the fragmentation of the adverse drug reaction system. Is that so?

Dr. CIARLA. That is right.

Senator KENNEDY. Could you very, very briefly summarize?

Dr. CIARLA. Back in 1969 when I joined the FDA, we had a workable Division of Drug Experience. We had many medical officers, good supervisors.

When the new group came in, of Dr. Edwards and Dr. Simmons, they began what was known as a reorganization. The reorganization was, in effect, a method of destroying, if possible, the Division of Drug Experience. We could see it coming. They subsequently hired a doctor from the University of Maryland, who became our acting consultant. In effect, he was Acting Director of the Bureau of Compliance, of Coordination, I am sorry.

He attempted to destroy us. He took practically all our medical officers out. He left us with nine medical officers, four of whom were nonoperable. When this did not accomplish his purpose, they got rid of the head and got a new head in, and just about a year and a half ago, a Dr. Harter was brought into the Office of Coordination I believe for the sole purpose of finally getting us wiped out.

He has put a lot of excess work on us, not essential to the problem of taking care of adverse reactions, in an attempt to demoralize the entire Division. He has done this very nicely. Two of them have resigned. Two or three more are in the process of resigning, if the burdens are not taken off of them. This pictures a rather gloomy state of affairs.

In the past we used to have approximately 20,000 adverse reactions coming into our unit. Since they have taken over, we now average about anywhere between 9,000 to 11,000. Now they want us to actually forget these, and just have some clerk in the office put them into our system, which would be useless for anybody to take out, and hope this will solve the problem of finally wiping us out.

Senator KENNEDY. What happened after your report came out?

Dr. CIARLA. I got no answer at all. Right after that I got orders from Dr. Crout to report to this new survey team, to examine nursing homes.

Senator KENNEDY. Nursing homes?

Dr. CIARLA. That is right.

Senator KENNEDY. What is your background on that?

Dr. CIARLA. I used to be public health officer, and I was also superintendent of public health for the city of Newport for 8 years. I do not think they knew anything about that.

Senator KENNEDY. There is a little silver lining in this. That is going to be up in Boston, is it not?

Dr. CIARLA. Yes.

Senator KENNEDY. Maybe you can consider it a promotion at least.

This has been an area in which you have been active for how many years?

Dr. CIARLA. Five and a half years now.

Senator KENNEDY. Thank you.

Are there any other comments? I think we have covered a number of areas.

I do not know whether anyone who spoke earlier wants to make any concluding comment or observation. Mrs. D'Acosta?

Mrs. D'ACOSTA. Senator Kennedy, there is one comment that I would like to make in connection with my transfer, which the record will show I requested, to the Drug Abuse Unit.

At the time of my transfer I was informed that I would be relieved of the duties of review. Subsequent to that, the period came for evaluation of Government employes. I think the record will show that at that point that I have had about 18 years of Government service and at no time have I gotten anything other than a very high rating for performance.

The supervisor under whom I was working of course was in the Drug Abuse Unit at that time. At the time of evaluation I had been under his immediate supervision, having had this interval under another supervisor. I had been under his supervision for less than 6 months.

However, excluding the intervention of my supervision by Dr. Glocklin, I had been under his supervision for some 2 years approximately. Dr. Tokas wanted to give me an evaluation of a certain order, which would be in line with all former evaluations that I had gotten for my performance. However, he discussed this with me and it was much lower than an evaluation that he had formerly given me as a supervisor.

I questioned it and he indicated to me that the rating that he had initially made would not be approved by the Division Director. I of course refused to acquiesce to the rating that the division director had indicated that he would approve, and after discussion with Dr. Tokas, he in fact agreed with me that he himself could not even give me the low rating that he had been advised to give me.

So a middle of the road was met. The rating that finally resulted was one much lower than I had through the years received, but admittedly I accepted because I quite honestly did not want any further reprisal. I have been transferred to the Drug Abuse Unit, and I was satisfied with the situation I was in, and quite frankly very happy to be in that unit of the Division, rather than in either Neuropharmacology Division or Psychopharmacology Division.

Senator KENNEDY. Very good. Before this panel leaves, I want to express again my very warm sense of appreciation for your comments this morning.

I want to emphasize that you have testified in response to subpenas. But what we have heard this morning is of enormous concern and distress to this subcommittee. Apparently there is a dual standard at the FDA.

We have heard of leaking of various files. We have heard of alterations and changing of files. We have heard how individuals who have been making these studies have been transferred during the period of review. I think this is a pattern which is of great concern to us, particularly when we consider that you are charged under the law with protecting the safety of the American consumer by guaranteeing the efficacy of these drugs.

It would appear that while you have been carrying out that responsibility you have been harassed and your scientific and technical judgment has been questioned. I think all of us understand there are instances where individuals may be right or wrong in terms of evaluation. Many of these questions are questions of judgment. But what we have heard this morning are a panel of witnesses whose background, expertise, and preeminence in these areas the American people greatly appreciate.

What the American people do not appreciate is the intimidation of dedicated public officials and the circumventing of procedures and rules that have been laid down by FDA itself.

I wonder why we should not look into various contacts that are made between drug companies and the FDA with regard to these various products? I wonder where those are listed? Should there not be rule-making procedures that establish that, conversations that are taking place?

These are some of the impressions that we gather. We are looking forward tomorrow to hearing Commissioner Schmidt. I was delighted that Senator Javits joined us, and I think he can be assured of unanimous feeling of both the Judiciary subcommittee and our Health subcommittee, that we will stand by you in making sure that the honest, candid, responsive answers you gave to this subcommittee this morning will not put you to disadvantage. We want to thank you very much for your appearance here.

Our final panel consists of Dr. Julia Apter, Dr. Roger Freeman, and Dr. Gerald Solomons.

Dr. Solomons is a professor of pediatrics at the University of Iowa, and director of the Children's Development Clinic at the University. He is a graduate of the Royal College of Physicians and Surgeons in Edinburgh, Scotland. He took his residency in pediatrics at the Royal Hospital for Sick Children in Glasgow.

Dr. Freeman is director of Services for Handicapped Children and Associate Professor of Psychiatry at the University of British Columbia, Vancouver, Canada. Dr. Freeman is a graduate of Johns Hopkins Medical School, 1958. He interned at McGill University. He did his residency at the Child Study Center of Philadelphia in child psychiatry. He was on the faculty at Jefferson Medical College in Philadelphia, and director of Services for Handicapped Children, St. Christopher's Hospital for Children; director of Child Psychiatry Clinic and Chief of Psychiatry, Temple University.

Dr. Julia Apter is a member of the Cardiovascular and Renal Advisory Committee of the FDA. She has a B.A. in Physics from the University of Pennsylvania; is a graduate of the Johns Hopkins School of Medicine, received master's degree in physiology from Northwestern University and a Ph. D. in mathematical biology from the University of Chicago.

She is the director of the Laboratory of Biomaterials and Biomechanics at the Rush Medical Center in Chicago, and an attending surgeon at Presbyterian St. Luke's Hospital in Chicago.

Dr. Apter also has a board certification in ophthalmology. She is also a professor of surgery at Rush Medical College.

Dr. Freeman, please proceed.

Dr. FREEMAN. Might I ask, because we were not subpenaed, whether what we say is also privileged here?

Senator KENNEDY. Yes. Why do we not swear you in?

Do you swear to tell the whole truth, nothing but the truth, so help you God?

[Drs. Apter, Freeman, and Solomons answered in the affirmative.]

STATEMENT OF JULIA T. APTER, M.D., PH. D., PROFESSOR OF SURGERY, RUSH MEDICAL COLLEGE, CHICAGO, ILL., MEMBER, FDA CARDIOVASCULAR AND RENAL DISORDERS ADVISORY COMMITTEE; ROGER D. FREEMAN, M.D., FORMER CONSULTANT, DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, OFFICE OF SCIENTIFIC EVALUATION, BUREAU OF DRUGS, FDA; AND GERALD SOLOMONS, M.D., DIRECTOR, CHILD DEVELOPMENT CLINIC, PROFESSOR OF PEDIATRICS, COLLEGE OF MEDICINE, UNIVERSITY OF IOWA, A PANEL

Dr. FREEMAN. Would you like for me to read my prepared statement?

Senator KENNEDY. It is a very effective one and very powerful one and we want to hear it all, but due to the lateness of the hour, I would appreciate you highlighting it.

Dr. FREEMAN. It would be satisfactory for me to comment as I go along?

Senator KENNEDY. Yes; we will include the statement in its entirety in the record at the conclusion of your testimony.

Dr. FREEMAN. I served as a consultant to the Division of Neuropharmacological Drug Products from about June of 1972 through June of 1973, although the actual period of work was only about five months.

We were originally called in, as I understood it, to prepare better guidelines for the evaluation of new drugs, so-called psychoactive drugs for children. As you have heard, Dr. Solomons was chairman of this task force, which consisted of two of us, and Dr. Eric Denhoff, a pediatric neurologist, who could not be here today.

I might add, as an aside, that this task is rather important because there has been a great deal of controversy over the prevalence, causes, diagnosis, and management of these childhood conditions, sometimes called learning disabilities or minimal brain dysfunction. There has been great political concern and public concern over the use of these drugs in schoolchildren, for school behavior and learning problems.

In fact, the Office of Child Development convened a special panel in 1971 to attempt to deal with these issues. I understood that we were to be involved in reviewing a drug, the drug mentioned this morning, Cylert, rather peripherally in terms of its being an example of the kind of thing which the agency and the drug industry were encountering.

At our first meeting, I believe on July 6, 1972, we received little if any orientation from the supervisory levels of FDA. I might add for someone coming into the agency who knows very little about it, this is a problem. It was a continuing problem.

We went to work on these guidelines right away. We then were told, to our great surprise, that the very next day there was going to be a meeting with personnel from the drug company and their consultants, which we were supposed to attend. We could not understand this, since we had just gotten started. However, it was common knowledge at the reviewing team level that the meeting was the result of company pressure because the drug had not been approved. We could not really sort this out at that point.

We agreed very reluctantly to this meeting, which could not be postponed, we were told, with the condition that we were just going to listen. We were not going to comment because we were not in a position to do so about this new drug application.

We were told that supervisory levels would be present and that this was OK, and that in fact this was the understanding about the meeting.

But this was in fact not the case. Nobody from supervisory levels showed up. We were left to carry the ball ourselves. The drug company was quite put out because they had a letter indicating that they were going to discuss their NDA. Even more curious, another company was present who was rather put out that an NDA of a rival firm was going to be discussed. The meeting then turned into a fiasco. We felt that we were being put on the spot and we did not know what to do.

We then attempted to contact supervisory levels, had great difficulty finding anybody. As I recall, I think it was Dr. Scofield who we finally turned up, who did come and indicated that there were some misunderstandings, that we have to come back to this at a later date. So we accomplished nothing at that meeting except becoming quite angry and quite upset.

We completed our guidelines. Then we started to examine the raw data. I might say personally that I have heard from the medical officer, Dr. Kennedy, some things about this new drug application which I found hard to believe. I believed that competent review was done and this would be carried through the agency. I found it hard to believe that some of the investigators were submitting data of this type. However, when we took an independent look at the raw data, I found that her concern was well justified.

Now, there seemed of course to be reluctance, as I heard this morning, on the part of the supervisory level to accept the team's recommendations. I do not remember exactly how it happened——

Senator KENNEDY. Why was that?

Dr. FREEMAN. I do not know. I cannot testify to state of mind of the higher-ups in the agency. But it was quite clear that if they did not approve the drug, they were, if not harassed, at least asked to go over and over things time and time again.

Senator KENNEDY. By whom?

Dr. FREEMAN. By their supervisors. In addition, there were, I believe, contacts directly to the medical officer from the drug company, which the medical officer could not turn off and could not avoid. So we decided that we would do something which I gather was unprecedented at that time, and that is to go through a page-by-page review of two cartons of files of raw data.

We came back to Washington several times to do this. We had difficulties with the system. We sometimes could not get the data. Our

guidelines which had been prepared, and we were told were accepted, to this day are in limbo somewhere. When we asked at various points where they were, nobody seemed to know.

Senator KENNEDY. Is that not rather a strange way to treat your advisers?

Dr. FREEMAN. We thought it was a very strange way to treat advisers; yes.

There was information which I understand it was legally required to be submitted, which had not been submitted, and I could not understand why it was taking so long, and why it was the medical officer who had to keep requesting this, and why supervisory levels did not take this into their own hands and make it quite clear to the drug company that this was necessary.

What happened gradually was that we developed a rather strange feeling among ourselves that there were forces at work which we could not understand, which we could not confirm, except at the reviewing team level. There was very strong mysteries between the reviewing team level and the supervisory level. It seemed to us we were being used in some way. We did not know what that was.

Without going into more details, I would say that the feeling that we developed led to the concern that when it came to the final presentations of the drug company, that if we let the supervisory levels know what we had in mind, this would be passed on to the sponsors.

Now, it is hard for people who have not been involved in this to believe the kind of atmosphere which existed. I have talked to many people about it since, and they do not believe it. The very night before this presentation, this is on September 28, we were called by Dr. Gardner and told that the format was to be changed, after all the work we had put in. He did not tell us why, as I recall, and we threatened to not be there.

With that threat, he agreed to just say a few introductory words and let us pursue our intent.

The September 29 meeting took place in an adversary atmosphere. It was quite clear to us, I think, and certainly to me that the burden of proof was not on the sponsor, but was on us and on the reviewing team, any one who felt that there were inadequacies.

Senator KENNEDY. Is that right? You mean that rather than the binder being on the drug company to prove that it is safe and efficacious, you felt it was on you to prove that it was unsafe?

Dr. FREEMAN. That is correct.

Senator KENNEDY. Is that not shifting the burden?

Dr. FREEMAN. As I understood the law and regulations, yes. But I want to emphasize also that we never felt that there was any sustained support from supervisory levels in this regard. We never knew where we stood.

After that meeting, which was attended by drug company people and some very eminent consultants of theirs, we were told something rather unusual by Dr. Crout, who did appear at that meeting for at least part of it. He said that this was a unique situation. He congratulated us on an unprecedented presentation which he suggested be replayed for the Commissioner. He was quite specific about this. This was said in Dr. Gardner's presence.

He also told us that the deficiencies in the NDA were not unusual. This was fine. I left thinking I had done a good job in a good cause, with a lot of difficulty.

However, subsequently a rebuttal came in from the drug company and investigator, and we did not get this directly, it was a rather peculiar situation, in which I requested, because I had heard about it, that we would be entitled to comment on that rebuttal and new material. There were some good points in that rebuttal and new material, which I felt needed comment as well as some points of misunderstanding.

We were not permitted to comment.

It was an unofficial submission, we were told.

Now, in addition to that, what happened was that the trade publication, the Pink Sheet, stated that the drug company had worked very closely with FDA on this drug, the implication being that this was an exceptionally good example. In fact, to my knowledge this was not the case.

It went on to say that lack of approval of the NDA was because of consumer group pressure. Never had there been the slightest indication that that was so. It also indicated that a second advisory group or ad hoc group was being appointed to re-review the medical officer's review. We had not been informed of this.

We were also to be isolated from that group. I was personally insulted at this way of handling things, and wrote a letter which I have made a part of the record to Dr. Crout, saying that I wished to send a letter to the new members of this new group. It may be of some interest that he only replied to this letter later, in that I gave the deadline—I gave him time to reply, and I got a telephone call from the secretary who could not, of course, discuss it with me, reading me a letter saying basically that I should not do this as a consultant to FDA.

He apologized for not informing us, because of course—indicating that there had been no pressure from the drug company.

Well, I have some comments here, but just to make them very brief——

Senator KENNEDY. When did you replay it for the Commissioner?

Dr. FREEMAN. We never replayed it for the Commissioner. We were never asked to replay it for the Commissioner. There was never any mention of this again. So that there was an obvious switch, from what we were told after that meeting by Dr. Crout and Dr. Gardner, than what happened subsequently.

This is again characteristic of this very unpleasant process.

I must say I learned a great deal from the experience. I would rather it had been otherwise. I feel strongly that one cannot accept summaries in lieu of raw data. We uncovered some things which caused us great concern, and I should tell this committee that there were published papers about the drug, which had inaccuracies in them, which we could not comment on, and we only discovered by looking at the raw data.

This raises the possibility, of course, that these deficiencies get into the literature. There were testimonial letters sent in by many eminent people, none of whom had seen the data, saying the drug should be approved, that it was needed.

These published papers, with their inaccuracies, of course, stimulate this kind of response from the medical community.

We are not in any position to say anything about it. I find this personally a very awkward situation.

I would agree with you fully that meetings between the drug company and higher levels of FDA should not take place without the medical officer present and without meeting—but without the meeting being recorded, and yet we were told repeatedly that this had happened.

I feel strongly that the medical officer's position is untenable, that good people are not likely to stay with the agency, or are likely to be transferred to other divisions, and I am frankly appalled at this situation and cannot understand the pressure which has apparently been mounted to weaken the system more and eliminate the review of raw data.

Senator KENNEDY. Is it your impression that the FDA is moving toward developing advisory groups, which will come in and periodically review different materials?

Dr. FREEMAN. In fact, Senator, it was my understanding when I was at FDA right at the beginning that this was the direction in which things were going, and these committees that may be appointed—very unlikely to review raw data themselves.

Senator KENNEDY. You only found this when you reviewed raw data?

Dr. FREEMAN. That is correct. There were discrepancies between data and summaries.

Senator KENNEDY. Who was preparing the summaries?

Dr. FREEMAN. The summaries are prepared by the sponsor who may be a drug company or who may be an investigator. In this case it was both.

Senator KENNEDY. Your testimony is that those summaries might be inaccurate; or at least in this situation they were inaccurate, but that they might be the basis for endorsement from some substantial or preeminent people?

Dr. FREEMAN. That is correct. Of course there is controversy over whether deficiencies are substantial or trivial. We were told the deficiencies were clerical errors.

Senator KENNEDY. What would you do if the FDA called you up again and asked you to be on an advisory panel?

Dr. FREEMAN. I would refuse under the circumstances that existed at that time. I found it personally a very disturbing experience.

[The prepared statement of Dr. Freeman and other material supplied for the record follows:]

STATEMENT FOR SENATE HEALTH SUBCOMMITTEE HEARINGS, August 15, 1974

by

Roger D. Freeman, M.D.

I served as a consultant to the Division of Neuropharmacological Drug Products, Office of Scientific Evaluation, Bureau of Drugs, Food and Drug Administration, from approximately June of 1972 through June of 1973. The following is a brief account of my activities and experiences.

A medical officer in the Division reviewed a New Drug Application (NDA) on a drug purported to be useful in the management of childhood hyperactivity and so-called "minimal brain dysfunction." As a consequence of her perusal of the raw data (as distinct from summaries submitted by the sponsors) she reportedly felt there were many deficiencies, and that better guidelines for the submission of such an NDA might be developed. She received approval for the appointment of a task force of consultants. Dr. Gerald Solomons, a pediatrician, was named as chairman. He nominated Dr. Eric Denhoff, a pediatric neurologist, and myself (a child psychiatrist) as co-consultants.

As I recall it, our task was to draw up Guidelines for Clinical Trials of Psychoactive Drugs in Children and Youth. The importance of this task should be placed in perspective. There has been much controversy over the prevalence, causes, diagnosis, and management of the childhood conditions noted. Medication usage has increased, there has been professional, public, and political concern over drug treatment of school behavior and learning problems, and a special Federal panel was convened in 1971 to deal with these issues.[1]

To return to the chronology: I understood that our Task Force might be involved peripherally in examining the review of the previously-mentioned

drug because it was a good example of the type of problem the Guidelines might resolve. At our first meeting, which I recall was July 6, 1972, we received little orientation from supervisory levels of FDA. We went immediately to work on the Guidelines. We then were told that we were expected to meet the next day with staff, officials, and consultants of the drug company. Because it seemed so premature, we could not understand the rush. However, it was common knowledge at the reviewing team level that the meeting was the result of drug company pressure because of delay in approval of the NDA. As new appointees, we were not in a position to sort out these conflicting opinions and forces. We agreed reluctantly to the meeting (which could not be postponed) with the proviso that we would merely listen, not comment on the NDA. In addition, we were assured that the supervisory level would be represented at the conference so we would not be alone, and that our conditions were satisfactory to both the FDA and the drug company. They were not. The company had been told their NDA would be discussed, and had a letter to that effect. They and their consultants, some eminent in the field, had flown long distances for this meeting. It was even more curious that another drug company had been invited; they were angry because they had no desire to listen to a rival firm's troubles. No representative of the higher levels of the agency appeared. We finally located one with great difficulty and expressed our displeasure with the situation for all concerned. It was agreed that there had been a misunderstanding, and that there would be another meeting.

We completed our Guidelines that visit, and had examined some of the raw data. Deficiencies seemed quite apparent and supported the medical officer's negative report, but there appeared to be reluctance on the part of the supervisory level to accept the team's recommendations. I do not recall the exact details of how we were asked and agreed to do a thorough review of

the NDA. On several subsequent trips the three of us did a page-by-page review of a substantial part of the 96 volumes of raw data in preparation for another meeting with the sponsors in September. But meanwhile we had difficulties with the system. We could not find out what had happened to our Guidelines, though we were told that they were approved. I still do not know. We heard reports that high-level drug company executives had met with FDA officials and had been assured that the drug would be approved, without the medical officer's presence at the meeting. Information which was legally required in the NDA had not been submitted and we could not understand why it had not been more forcefully requested. At times it was even difficult to have access to the volumes of raw data.

Gradually I believe we all developed the feeling that we were in the middle of a palpable but indefinable vortex of forces. The reviewing team showed strong mistrust of the supervisory level; morale was low. It seemed that we were being used in some way which was quite different from our original expectations.

We developed a format for the final presentation to the sponsors, but were told the night before that it was to be chaired by Dr. Gardner of FDA, not Dr. Solomons, and that he had a different agenda in mind. Because we literally threatened to boycott the meeting and the sponsors would never have tolerated another fiasco, we were permitted to proceed as planned.

The September 29 meeting took place in an adversary atmosphere. I never felt that the burden of proof for safety and efficacy was on the sponsors, but rather that the medical officer and reviewing team, including ourselves, were on the defensive. I should mention also that prior to this meeting quite a number of letters had been sent by well-known investigators and professors, supporting the drug, the NDA, and the need for the drug. None of these people had reviewed the raw data, but I believe had received summaries from the sponsors.

We presented our conclusions that the NDA was inadequate as measured by adherence to the approved protocol. Not only had there been discrepancies between summaries and raw data, but published reports in medical journals were inaccurate, yet used to support the NDA. These were attributed to "clerical error." At the end of the meeting we were told by Dr. Richard Crout, Acting Director of OSE, in the presence of Dr. Elmer Gardner (Director, DNDP), that it had been a precedent-setting presentation which he wished to have re-played for the Commissioner. We were also told that the deficiencies uncovered by us were not unusual in NDAs. I personally left with a feeling that we had worked hard in a good cause.

I am not sure of the events subsequently, but they were a surprise. Apparently after prompting by the reviewing officers, a non-approvable letter was issued on November 21, 1972. The sponsors then submitted a rebuttal and new material, some of which should have been available in the NDA and might have altered part of our conclusions. I recall that it was difficult to get a copy of the rebuttal, since it was deemed "unofficial," and we were not permitted to comment upon it. Meanwhile the trade publication known as "The Pink Sheet" explained the lack of approval as due to pressures from consumer protection groups. Without informing us, it was decided to appoint another committee to re-review the medical officer's review. We were to have no contact with this new committee. The final report and other information indicates that the new committee had some disagreement within its own ranks and with us. I wrote a letter deploring the way this situation had developed which is attached to this statement.

Comments

I have strong feelings about the unpleasant process which we went through. I would never wish to repeat it. However, it is important to under-

stand that this has nothing to do with matters of scientific judgment which are always open to disagreement and interpretation. It is clear to me that the laws, regulations, and administrative structure should protect the evaluation process, insofar as possible, from the forces we encountered. I do not believe we or the reviewing team were able to do a proper job. That this is no isolated experience is supported by three books on the FDA which I only read afterwards and conversations I had with medical officers in other divisions of FDA.[3-5]

This statement is not the place to argue about the philosophy of drug regulation. I merely wish to state that I do not believe it is safe for the country to remove the requirement that efficacy as well as safety be substantially demonstrated, nor is it safe to give up reviews of raw data and trust sponsors' summaries. Sloppiness, bias, and occasionally outright fraud can be obscured by statistical pyrotechnical displays.

It may not be unfair to compare the pressures placed on medical officers with those suffered by air traffic controllers. Certainly the responsibility is no smaller, though less dramatic. Their morale is crucial. Rapid turnover leads to diminished expertise we cannot afford. They must be protected from inappropriate pressure to approve a drug. Surveys have been done.[2] Many of the reasons for low morale have been identified. I sincerely hope this Subcommittee can help solve the problem.

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References

1. Dept. of HEW, Office of Child Development: Report on the conference on the use of stimulant drugs..., 1971. (Repr. in J. Learning Disab. 4: 59, 1971).
2. Federal Times: FDA scientists hit industry pressures. Aug. 9, 1972.
3. Fine, R.A.: The great drug deception. New York: Stein & Day, 1972.
4. Mintz, M.: By prescription only. Boston: Beacon Press, 1967.
5. Turner, J.S.: The chemical feast. New York: Grossman, 1970.

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(604) 228-2032 (office)

March 13, 1973.

Dr. Richard Crout,
Acting Director, O.S.E.,
Bureau of Drugs,
Food and Drug Administration,
5600 Fishers Lane,
Rockville, Maryland.

Dear Dr. Crout:

I would like you to know my reactions to the "Pink Sheet" report on March 5, describing the formation of an "Ad Hoc Committee" to re-review the Cylert NDA.

First, I am puzzled by the statement that "Abbott worked very closely with FDA throughout the review procedures." It was my recollection that there were unauthorized changes in the Conners protocol which Abbott admitted at our September meeting, and that they failed, for many months, to provide some requested data.

Second, the "Pink Sheet" goes on to say that pressure from consumer groups "reportedly weighed heavy in FDA initial decision to turn down NDA". You and I know this is complete rubbish. Where did this idea originate?

Third, and perhaps more important, you told us we had set an important precedent by reviewing the raw data and confronting drug company officials and consultants. I thus find it difficult not to take it as a personal and professional insult that we have: (1) not been permitted to reply to the Conners and Abbott rebuttals to our presentation, despite my official request to do so; and (2) not been informed that you intended to go over the heads of your medical reviewing team and consultants.

After the September meeting we had a long talk in the presence of Dr. Gardner. You originated the idea, with no dissent from him, that we "replay" our presentation for the Commissioner. You also indicated that you would personally see to it that undue drug company pressure would be resisted in future. Now the rebuttals have come in. They are called "un-official" so we have, apparently, no right to comment. Yet I assume they

are the basis for the company's "appeal" of the non-approvable decision.

You will recall that Dr. Conners admitted he had erred in reporting on the number of cases in his study, the obtaining of both school reports and physical data. He claimed this was only reported falsely in his article in "Pediatrics" which he surprisingly termed "preliminary". However, these errors were not removed from his subsequent paper in "Psychopharmacologia".

In his"rebuttal", Dr. Conners made a major point of the psychosocial factors which the consultants felt clearly violated the protocol standards in many cases. He reduced our point to the absurd, suggesting that since a bad environment interacts with brain dysfunction (a point well made by the Isle of Wight study years ago), any degree of noxious influence, including psychotic parents, multiple foster homes, battering, etc., is compatible with inclusion. Again, <u>despite the protocol</u>.

You will remember that we did not like the protocol, but sought to avoid controversy by accepting it and only attempted to measure adherence to its standards. Several good points were made in The Conners and Abbott rebuttals, especially since new information was provided which should have been (but was not) available to us for review. It would have been useful for all concerned had FDA permitted comment from us. If we were incompetent, we should not have been appointed consultants. If our work was unsatisfactory, we should have been told so. Instead, we were commended until (apparently) Abbott brought pressure to bear.

I rather doubt that the ten members of the Ad Hoc Committee will be provided with all the relevant information or have the time to review, as we did, all the unselected raw data.

In the belief that the Ad Hoc Committee members should know what they are getting into, I intend sending a copy of this letter to each of them. Because I wish, as always, to be completely fair, I will delay doing so for ten days from the date of this letter. If there is any compelling reason why I should not send this letter, please call me at the above-listed number.

Yours sincerely,

Roger D. Freeman, M.D.,
Associate Professor,
Director of Services for
Handicapped Children,
Division of Child Psychiatry.

cc. Dr. Henry Simmons.
cc. Dr. Elmer A. Gardner.

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March 23, 1973.

Daniel X. Freedman, M.D.,
Department of Psychiatry,
University of Chicago,
950 East 59th Street,
Chicago, Illinois, 60637.

Dear Dr. Freedman:

RE: FDA AD HOC COMMITTEE ON CYLERT

I very much regret the need to send the enclosed letter to the Committee members, who will undoubtedly wish to be objective and avoid possible contamination. However, I am concerned that bias will not be avoided by isolation from us.

We were originally asked to come to FDA to prepare guidelines for protocols for new studies (which we did). Despite our objections, we were immediately (and without sufficient preparation) thrown into a confrontation with Abbott and its consultants and investigators. FDA higher echelon officials disappeared and were only brought on the scene by justifiably irate Abbott representatives who had been given a different agenda for the meeting than we were.

We were later placed in the position of not only checking up on the findings of the medical reviewing team, but also confronting the company, its consultants, and the investigators. We only acceded to what we considered to be an unnecessary and morale-lowering procedure (for the FDA team) because of some of the major irregularities uncovered in our review.

This information, sketchy as it is, may help your committee to understand the structuring of our September meeting with Abbott.

I sincerely hope you can sort out the scientific from the political and financial issues involved.

I am sending along two extra copies of this letter for Drs. Schulman and Cohen, whose addresses are not immediately available to me.

Yours very sincerely,

Roger D. Freeman, M.D.,
Associate Professor,
Director of Services for
Handicapped Children,
Division of Child Psychiatry,
Consultant, F.D.A.

RDF/mft
Enclosures

cc.: Dr. Eric Denhoff
-> Dr. Gerald Solomons
Dr. Barbara Fish
Dr. C. James Klett
Dr. Robert Reichler
Dr. Robert Moore
Dr. Reginald Lourie
Dr. Robert Sprague
Dr. Morris Lipton

Senator KENNEDY. Dr. Solomons?

Dr. SOLOMONS. I can heartily confirm everything that Dr. Freeman has said. This was one of the most frustrating, embarrassing, and depressing experiences I have ever had in my medical career. I think that there are one or two things that I could perhaps emphasize, and that is the discrepancy between the raw data, the summary and what is published, the fact that this can be dangerous because it does, as has been said, cause a great deal of publicity and a certain amount of public pressure to release the drug which may have been inadequately evaluated.

I was rather concerned about the long-term evaluation of drugs with regard—of that particular drug with regard to the children. Some of the children, the long-term followup, as delineated in their own protocol, had not been carried out, and this was of great concern to us.

Senator KENNEDY. Whose interests were really being served here? Do you think the interests of the drug companies, of the sponsor of the drug, were weighing more heavily than the public interest, the people were going to be affected, the children that were going to be affected by this?

Dr. SOLOMONS. Senator, I would like to be fair about this. I realize that when you are in this type of area, you are in a rather emotional climate, that there are some people who believe that there is a miracle drug that is going to work. I believe that in cases where the disease or the entity being treated is life-threatening, that these considerations should be weighed and perhaps a little bit more flexible.

But in a case like this in which there was, first of all, controversy about the syndrome existing in scientific circles, and secondly the fact that long-term evaluation of the drug had not been really delineated and proved safe, that there was no great rush to get in on the market, because there were at least two other drugs that had been proved to some extent and not completely relatively safe, and relatively efficacious in certain circumstances.

But the need here to rush it into marketing, if you like, or approval, to me seemed to serve the interests of the company rather than the interests of the children.

Senator KENNEDY. Could we review your complete statement, Doctor? It will be in the record, but let us just review those conclusions. I thought they were extremely useful. I want to thank you for giving your testimony to us. I read it last night. It is a shocking, shocking indictment of the practices and procedures. But let us just go through those conclusions, and we will include your statement in the record at the conclusion of your testimony.

I would just be interested in whether your colleagues would agree. Do you want to just read those?

Dr. SOLOMONS. Yes.

My first one was that my 5-month—and I must emphasize this was a 5-month evaluation with one drug, plus formulation of guidelines—my 5-month association with the FDA led me to the belief that in this particular instance—and I emphasize that—the Administration officials—and I must emphasize that, the lower echelon of reviewing committee level, we had nothing but praise and commendation for the diligence of the people concerned——

Senator KENNEDY. I am glad you mention that, because I think that is important.

Dr. SOLOMONS. And that the Administration people were not particularly interested in what we were doing initially, until we started coming up with what we considered to be negative or critical findings.

We also had the belief that all our deliberations were being conveyed on to the drug company, because of questions we were asked by company representatives and consultants at the two meetings we mentioned before.

We did become, frankly, paranoid that our deliberations were being given to individuals so that predetermined explanations perhaps could not be made.

Now this bothered me and the others, because this was not the climate in which I had been involved. In consultation previously in medical circles it was my experience that you were there in a combined effort for the good of the children and to make sure that whatever you were using was at least safe. One of the prime concerns of treatment, I think, is that it should do no harm.

The administrative officials appeared to have little interest in our deliberations until some negative findings were uncovered. I think that goes back to what Dr. Freeman said, that when we first arrived we were unnoticed.

The professional members of the staff, particularly in the lower echelon, were exceedingly helpful and competent, but their morale was low, and they were extremely skeptical of any commitments or statements made by administrative personnel.

We disbelieved them. We found they were correct, as time went on. We were aware also of apparent harassment of the Reviewing Medical Officer.

We also found apropos of that that when we tried to obtain data, difficulties were put in our way. We could not get it. It was difficult for us to get a transcript of the meetings that we participated in. Why? Because there were certain regulations which remained kind of nebulous. We then put together, as you heard, guidelines for clinical trials of psychoactive drugs in children and youth. We spent a great deal of time over this. We think that those guidelines are a good basis for discussion among professionals in the field for a definitive formulation for procedures and practices in this area.

We were told—as a matter of fact we put these things basically together in 48 hours. We mulled them over for a period of approximately a month. We wrote them out and submitted them. We were commended for something that was called superb, that verbally had been approved up in the Division level, and that they would be implemented as soon as possible. They wanted to show them to some other people, which was understandable.

We have never seen those guidelines. We asked if we could publish them; the answer was no.

At one particular meeting we asked where they were at that particular time, and not one person in the Administration could tell us where they were. I have never heard. That was 2 years ago.

May I also say that there was a committee formed by the American Academy of Pediatrics to come up with similar guidelines, formed

approximately 2 to 3 years ago, and they too have never come up with any guidelines.

It is my considered opinion that in this particular instance investigations were inadequate, and I am talking about the Cylert. Crucial long-term data on safety and efficacy were collected in a haphazard fashion with some potential risk to the health of the subjects.

As I mentioned before, there might be some mitigation if the disease entity being studied were fatal or even critical. It is not.

I respectfully suggest that the committee study the guidelines that we formulated.

I would like to close by quoting from the preface to those guidelines.

"The climate of the times, the demands of the public and the potential for abuse of psychoactive drugs"—and I must say that there is abuse of psychoactive drugs by professionals—"necessitate a protective and objective attitude on the part of the FDA in order to safeguard the development of children and youth in the United States."

[The prepared statement of Dr. Solomons follows:]

PREPARED STATEMENT OF GERALD SOLOMONS, M.D., DIRECTOR, CHILD DEVELOPMENT CLINIC, PROFESSOR OF PEDIATRICS, COLLEGE OF MEDICINE, UNIVERSITY OF IOWA

I was approached by Dr. Carol Kennedy of the Bureau of Drugs in March or April, 1972, and asked to consult with the Bureau regarding problems involved in the evaluation of drugs used in the treatment of symptoms of minimal brain dysfunction. There was concern regarding poorly designed and uncontrolled clinical trials and the lack of information regarding long term effects of drugs on personality and the physical growth and development of the child.

A New Drug Application (NDA) under evaluation seemed to illustrate some of the problems which were encountered by the FDA Reviewing Medical Officer in the evaluation of clinical drug trials of this type. I was asked to review this protocol and the forms used in the study and then come to Washington on May 3, 1972 to discuss it with the Reviewing Medical Officer.

I did this and wrote a report dated May 18, 1972, which independently arrived at similar conclusions of the Reviewing Medical Officer. I found the protocol lacking in objectivity and definition and no reliable conclusions could be drawn from the data supplied.

I was asked subsequently to chair a Task Force consisting of Eric Denhoff, M.D., Professor of Clinical Pediatrics at Brown University, Providence, Rhode Island and Roger Freeman, M.D., Associate Professor of the Division of Psychiatry of the University of British Columbia in Vancouver, Canada. Our charge was to formulate guidelines for clinical trials of psychoactive drugs in children and youth. The Task Force met in Washington on July 6 and 7, 1972. During that time, with consultation with professionals in the Bureau of Drugs, we arrived at acceptable guidelines which we refined over the following month and finally approved and reported on August 4, 1972.

Much of the information to formulate these guidelines were obtained from a review of the previous mentioned New Drug Application as well as our own experience in research in this very complex and subjective area. On July 6, the first day that the Task Force had ever met, we were asked to meet the following day, July 7, with representatives and consultants of the drug company which had submitted the aforementioned NDA. To us, this seemed unusual and we asked for and received an explanation which was rather nebulous. We were assured that this was purely in order to obtain input from a drug company with regard to its difficulties in experimental design and general problem areas. This would help the Task Force to consider all sides of the question. We agreed to this after learning that another drug company, also in the production of psychoactive drugs, would be present.

The meeting was held the following day, July 7. We commenced without any member of the administration staff being present because not one could be obtained. Our inquiries were shunted from one office to another and it was not until a personal demand was made that an administrative officer appeared. The drug company representatives and consultants of the firm submitting the NDA were highly indignant and angry because their communication from the Bureau of Drugs indicated that the meeting was to discuss their protocol and our evaluation of it. They had received information that at least my review and possibly that of the Task Force was critical. The other drug company had been told that it was to discuss guidelines and they would not have been present if another firm's NDA was being discussed. The administrative officer gave a weak explanation for the confusion and apologized for the apparent mix-up. Despite the protestations and insistence of the drug company for us to discuss their protocol, we refused and the meeting was adjourned without any meaningful discussion.

At the July 7 meeting, the Task Force, after completion of formulation of the guidelines, was given the charge of evaluating the previously mentioned New Drug Application for efficacy and safety. The Task Force met on August the 3rd and 4th, after each member had worked independently in his own locale and agreed to review the raw data of the New Drug Application. This appeared to cause some consternation in the Bureau because this was highly unusual; as a matter of fact, we were told it had not been requested before. After a great deal of discussion and high level decision, the data were supplied in a small hand truck comprising approximately one hundred and forty large volumes. ~~This~~, The Task Force commenced to review more than half of the raw data on a page by page basis.

It was at this time that I personally began to sense a lack of cooperation if not obstructionism against the Task Force's evaluation. It appeared that our deliberations were being relayed to the drug company after confrontation with administrative officers. Professional personnel who had been involved and enthusiastically supported our findings and recommendations were assigned to other projects. All of a sudden ~~an extreme disinterest in~~ our evaluation seemed to become most important. Our guidelines, we were told, were superb and had been verbally approved by the head of the division and, hopefully, would be in operation in the very near future. To this day, I and the Task Force, have heard nothing more regarding these superb guidelines nor, to our knowledge, have they been discussed.

We were asked to have another meeting during August 3 and 4. Our deliberations led us to the conclusion that there were many major deviations from the protocol and that published reports on part of the study did not correlate well with the raw data we had examined. We decided to continue our evaluation. The Task Force met in Washington on September 27, 28, and 29, 1972, working practically throughout each day documenting in detail what we considered to be deviations, including the preparation of approximately 90 slides visually illustrating these deficiencies according to our interpretation. We were asked to meet with representatives and consultants of the drug company to discuss the protocol and our findings. This, we knew, was highly unusual and a second attempt for us to justify supposedly our recommendations. We agreed to do this providing that I was Chairman of the meeting, the Task Force presented all its data without any interruption in the morning and that the drug company and its consultants would have an equal time opportunity to rebut our findings in the afternoon. This was agreed to by the administration and presumably the drug company. There were many attempts to elicit from us our finding which we refused to do because we had the feeling that they would be transmitted and prepared explanations could then be predetermined. The meeting was scheduled for 10:30 A.M. on September 29, 1972.

At 10:45 P.M. on September 28, the Task Force was working at the home of the Bureau Medical Reviewing Officer who returned a phone call to one of the administrative officers. Dr. Freeman and I participated in this phone call on the extension phones in the house. The administrative officer stated that the procedure for presentation the following day had been changed. He had been instructed to chair the meeting. That a new agenda, including an introduction by himself of the history of this situation and that the reviewing officer would have to re-present her material to which the sponsor had already objected. This to us appeared to be a complete waste of time and in our view, an attempt to reduce the amount of time available to us to present our material. I informed the administrator that the Task Force would not attend the meeting if he

carried through with this intention. If he agreed to leave things as they were and then in any way attempted to interfere with our presentation, the Task Force would walk out. It was then agreed that no interference would take place and that the administrator be allowed to make a few brief introductory remarks and chair the meeting.

The meeting was held the following day. There was no interruption of our presentation. In the afternoon there was some non-specific discussion and the representative of the drug company stated that it would not be possible to make an adequate response until many of the specific points had been gone into and that another session at a future time could be arranged.

Dr. Freeman was told by one of the higher echelon administrative officers in the Bureau, who attended the session, that this was one of the most effective presentations he had ever seen, that it was certainly one of the most intensive investigations and that it was superb. He asked if we would "replay the presentation" for the Commissioner. These remarks Dr. Freeman conveyed to the other two members of the Task Force in a written communication.

Despite the above commendations, I received notification on March 19, 1973, that a non-approvable letter regarding the drug had been sent to the company and that as they protested some parts of our statement, a panel had been selected by the Neuropharmacology Advisory Committee for review of the application.

In conclusion, may I delineate my concerns.

1. My five month association with the FDA led me to the belief that, in this particular instance, the administration officials did not seem to be particularly diligent in determining deficiencies in the New Drug Application.

2. We had the belief that all our deliberations were being conveyed to the drug company because of questions we were asked by company representatives and consultants.

3. The administrative officials appeared to have little interest, in our deliberations until some negative findings were uncovered.

4. The professional members of the staff, particularly in the lower echelon, were exceedingly helpful and competent but their morale was low and they were extremely skeptical of any commitments or statements made by administrative personnel. This, we found to be perfectly true over a period of time. We were aware also of apparent harassment of the Reviewing Medical Officer.

5. Administrative personnel appeared extremely reluctant to be involved in any confrontation with the drug company representatives and, indeed, we had almost to drag bodily an administrator to be present at our initial meeting with the company.

My further concerns are spelled out succinctly in the Task Force Report on the "Formulation of Guidelines for Clinical Trials of Psychoactive Drugs in Children and Youth" and the Task Force evaluation of the New Drug Application.

It is my considered opinion that in this particular instance, investigations were inadequate. Crucial long-term data on safety and efficacy were collected in a haphazard fashion with some potential risk to the health of the subjects. There might be some mitigation if the disease entity being studied were fatal or even critical. However,

the syndrome under review is not life threatening and there are other medications available that are equally, if not more, effective.

I respectfully suggest that the Committee study the guidelines formulated by this Task Force. I would like to close by quoting from the preface of those guidelines.

"The climate of the times, the demands of the public and the potential for abuse of psycho-active drugs necessitate a protective and objective attitude on the part of the FDA in order to safeguard the development of children and youth in the United States."

Gerald Solomons, M.D.
Director, Child Development Clinic
Professor of Pediatrics, College of Medicine,
University of Iowa

Senator KENNEDY. Dr. Apter?

Dr. APTER. I will just abbreviate my testimony and make additional comments.

I am a member of the FDA Cardiovascular Renal Disorders Advisory Committee and I am to serve from July 1972 to July 1976.

So that I have already testified for 2 years. But, besides serving on that committee, I have been a consultant on the drug side that you have just heard discussed and also on hexobendine that you have heard discussed this morning.

I accepted the position only because I feel that the FDA protects the consumer but because I feel the FDA protects physicians as well.

The way in which consumers are protected is not only because they have drugs that are unsafe, kept out of the market, I thought, but also because drugs that would be tested for efficacy and that would protect the consumer or patient from being treated with a drug that would not be appropriate for the disease that they had and therefore would be exposing them to additional danger.

At the first two meetings that I attended on September 8 and November 29, 1972, my ideas about testing effectiveness and safety of drugs for particular uses were presented.

The guidelines we developed strengthened my pre-employment impressions of the functions of the FDA.

Before our third meeting on February 14, 1973, I had been called on by two of the medical officers of the FDA to help with Cylert and hexobendine.

Let me say with respect to the Cylert investigation and meeting that I attended on November 29, I thought that the presentation by Drs. Fuller and Solomons were exactly what I needed to help me decide upon the efficacy of the study, the way in which the study had deviated from protocol and safety.

Then when the ad hoc committee was formed to be convened in Chicago where I worked, I also, however, was isolated.

I did speak to Dr. Freeman who was the chairman of the ad hoc committee asking him why he had approved the drug and I got—that is approving said use in hyperactive children, and I was told, well, Harvard is a good place and Dr. Eisenberg, who is the investigator in that investigation was a good person.

I feel I was beginning to get the feeling from the investigation in Cylert, that not only were the drugs being presented to the public so that the consumer was getting additional curiosity about its possibility, a way of managing a particular disease, but the physicians were getting information that was not reliable.

It was not being reviewed by the FDA, it was not being supervised and, indeed, in the case of Cylert it was actually misrepresenting the data.

So these experiences convinced me that supervision of the investigations conducted by drug companies really has to be put into the law, it has to be enforced and the investigations have to be according to prewritten protocols.

The supervision, I feel, would prevent the use of new drugs for clinical use before it would be approved by the FDA and I feel it would result in a more reliable investigation, but most importantly,

it would prevent risk to patients that would be used in impractically conducted trials.

How can a physician tell a patient what kind of a risk they might be exposed to if they were used in this trial, unless the physician knows what those risks are and hopes to find out by testing the drug adequately in animals, at least.

I also am opposed to our looking to Europe for leadership in the use of drugs.

For example, Cylert and hexobendine both have been used in Europe and were not considered by us to be adequate, especially hexobendine.

It was allegedly effective for some cardiovascular diseases in Europe, but here it was proven to be ineffective.

Besides that, European standards for establishing safety are much more stringent than the FDA.

Senator KENNEDY. You think there is a drug lag?

Dr. APTER. I do not believe that there is a lag between the time that a drug is considered possibly effective and the time that it is actually put to clinical use. I am not sure that the lag is even long enough.

I do not think that we need many of the drugs that the Europeans are using. If you mean by drug lag, that the lag is longer than it ought to be, I have to say absolutely not. There is, of course, a lag.

There has to be a lag between the time that you decide that a drug might be useful and the time you put it to use because you have to test it for safety in animals and test it for efficacy, and then test it for efficacy in patients that are given truly informed—that give their truly informed consent.

One of the meetings of our committee took place, that is the February 14, 15 meeting, took place in the Oxford Room of the St. Francis Hotel in San Francisco.

I attended that meeting with great personal sacrifice because I was going to be giving my report on the ocular toxicity of hexobendine.

Yet, when I arrived I found no transcript was going to be kept and then because I asked for a transcript, the meeting was canceled by the executive secretary.

I had asked for that transcript in compliance with Public Law 92–463, a copy of which I happened to have at the meeting.

I was very disappointed to see that both the chairman and the executive secretary, besides making me feel very uncomfortable at the time of the meeting, because of asking for the transcript, we had always had transcripts, and for some reason in this case this was considered reprehensible.

Not only did they make me feel uncomfortable in the meeting, but they also put in the minutes that the meeting had been cancelled as a result of an atmosphere that developed because of my asking for the official minutes.

So this convinced me that maybe FDA staff employees must be kept up-to-date concerning FDA related legislation and must act in compliance with it. I certainly think that advisors who insist on compliance with laws should be treated courteously.

It did make me think as did Dr. Freeman, that some inexorable forces were operating to keep those of us who want openness and full records to be kept, to not have our say.

It reminded me of the fact that although I started my service for the FDA thinking that we were going to be running protocols and protecting the public, Dr. Warren, the chairman of my committee, asked me to have a cocktail with him the night before our first meeting, and spent the time, while I was drinking ginger ale, I guess, telling me that they were having a lot of trouble with FDA people, not the higher administrators, but the lower people which I now must assume to mean the medical officers.

I, on the other hand, found the medical officers that I have worked with exceedingly responsible and their ideas in ways of handling research and investigation into the effectiveness of drugs precisely like my own.

The meeting of April 13, 1973, was special, that was devoted to the study of the consideration of propanolol in the treatment of angina pectoris.

Before the meeting I received about 700 pages of reprints and manuscripts concerning propanolol for this use.

It was supplied to me by Ayerst Corp., which is a drug company.

I read all, though all of the material, and immediately I was extremely curious and especially read the 33 reprints that had been labeled by Ayerst as "controlled studies."

Later, I was assigned especially to reprints 1 through 12 of the group of 33.

I found that although I had been asked to state about these papers: "Does the study qualify as adequate and well controlled?"

"What efficacy in angina pectoris is demonstrated?"

"Is there concern for safety?"

I found that none of them qualified as adequate or well controlled, and they did not demonstrate angina.

And there was concern for safety, since some of the patients with angina were made much worse with propanolol in that their withdrawal symptoms were worse, even fatal.

This tendency of propanolol has apparently been noticed previous to my having brought it to the attention of the advisory committee, and that there is a warning in the package insert, that says it should be withdrawn gradually and then it says it should be withdrawn gradually over a period of 2 weeks.

But I know of no evidence that supports that that would protect the patients any more than sudden withdrawal would if those patients are having an adverse reaction to withdrawal.

And in any case, if you have a drug that is recognized as having withdrawal symptoms, you must be very careful how you do the statistical analysis of any data that would be comparing patients who are on placebo worse because they have been taken off of the drug or are patients on placebo worse than those on the drug simply because the drug does make them better?

That would have to be established and not a single one of the 700 pages addressed itself to that particular point.

Indeed, there were many of the reprints that said specifically that the patients were made much worse after they were withdrawn from the propanolol.

This experience convinced me and I get more and more convinced that raw data from new drug applications has to be available to us scientific advisors if we are to evaluate the drugs properly.

It drew my attention again to the fact that investigators were exposing hundreds of patients to risks associated with a drug, even though dangers of such exposure was specifically pointed out in the literature.

How could there have been hundreds of reprints in which 20 to 30 patients at a time were being given propanolol for angina pectoris without some supervision, without some guidance by the FDA.

And this——

Senator KENNEDY. The doctors feel that they ought to be able to do whatever they like.

They know the best how to proceed and they do not want somebody in FDA to tell them how to practice medicine.

Dr. APTER. On the other hand, the International Institute of Health has done trials up to this date and finds that supervision is absolutely essential.

First, the studies have to be prospected.

There has to be protocol that is detailed and approved by the group that will be involved and all of the people involved have to accept that protocol and agree to a by-product, and all records must be written and no opinions after the fact can be considered, otherwise it then becomes a retrospective study which cannot be accepted in support of the use of any kind of a drug or in treatment.

So that while there may be physicians who feel this way, I think we ought to find out whether those physicians have had—how much experience and training they have had in statistics because I know of no statistician that would say that that would be an adequate way to investigate a new drug or new use for a drug.

It was this kind of experience that convinced me that the position of a lone statistician on a committee is not as effective as it ought to be.

I was the only statistician in my advisory committee.

There were often other statisticians present during the time that we were reviewing drugs, but they were not voting members of the committee.

I would have liked to have seen and still would like to see more statisticians. I would like to see more people who are scientists and not themselves involved in giving these drugs to patients.

I would like to see more people who are not close personal friends of the people who are serving as investigators for the drug companies, to be on the advisory committees and I cannot stress too strongly that I think that publications of investigations should be withheld until FDA review to prevent widespread use of the drug and then the FDA would have to curtail or supervise it more widely.

In the case of propanolol, we see so many physicians were using the drug for angina on the basis of these unsupervised publications that the FDA felt it had to control that use. And we were told that that was our job.

We had to say, should we change the package insert; should we—and insert some specific guidelines to physicians so that they will not misuse the drug?

We would certainly not be recommending it for use in angina, that was said over and over again during the meeting, or we could say that we were not going to change the packaging service, or we could say that we would change the packaging and recommend.

We all voted against the recommendation in any form.

I voted not to change the packaging insert since on the basis of a careful review several years before propanolol had been ruled out, had been disproved for use in angina. I saw no information to support a change in that point of view.

It looked as though the physicians were using it and they were putting pressure on the FDA or maybe the detail men were advising the physicians to use it and therefore, they were putting pressure on the FDA.

I heard no contrary statements to this evaluation of mine at the time.

On May 8, 1973, I attended a meeting of the FDA Ophthalmic Drug Advisory Committee to report on my evaluation of hexobendine and its apparent tendency to induce cataracts in humans as in dogs.

I recommended the use in a trial and I submitted a written report.

It has never been checked to me as having been included in any other reports on hexobendine.

I asked that they, the patients, since they had already been examined twice, double-blindly, and reportedly had a high incidence of possibly drug-related cataracts, according to the doctor who examined them, that a further study was needed.

Two advisors of that committee expressed opinions similar to mine and I decided maybe voting is not the best way to reach evaluation of the drug.

Senator KENNEDY. Was your advisory committee misrepresented?

Dr. APTER. With respect to propanolol, since we have gone specifically on record as not recommending the propanolol for angina, and yesterday I saw a letter signed by Dr. Crout and dated September 4, 1973, and sent to Ayerst, saying that the advisory committee had recommended the drug for angina.

Senator KENNEDY. That is misrepresenting your conclusion?

Dr. APTER. It misrepresented the advisory committee's decision, yes. I feel that the FDA could recommend it if they wanted to dispute what our advice is, but I do not think that they should say that the advisory committee has recommended it when we have specifically not.

Well, this experience also convinced me that industry-supported investigators be selected so that they have adequate time to examine patients because it so happened that Dr. Emery, who had an ophthalmologist, whom I would have trusted, and who reported this high incidence of possibly drug-related cataracts on a double-blind study on them, in this meeting, said that he had been busy and tired at the time that he had made those notations on the original record, and therefore they should not be trusted and if that is so, then the investigators should have adequate time to examine patients thoroughly before reporting their evaluations and they should be held accountable for the records that they keep.

We found this was needed in Cyclert as well as hexobendine.

At the meeting of September 20 and 21, in Washington, we discussed the atropen and there we were asked to—well, the committee did vote to approve the action of further clinical trials, although when I raised the question of safety of the atropen, it was decided, well, we already knew it was safe because according to the company's sponsoring it, millions had been sold in Europe.

I do not and still do not feel that that is adequate proof of safety.

I would like to see FDA officials insist on their own that there be more evidence for safety rather than testimonials for safety.

On November 30, I received a letter asking me whether I would be willing to participate in the IND and NDA's by the staff, even though that would mean that I must have a lockable file cabinet in my office and must not reveal any trade secrets.

I can tell you what I think the purpose of our advisory committee, that was to be the subject of one of the subsequent advisory meetings, but somehow the time of that meeting kept getting changed and finally fell on a date which I had already said would be impossible for me to make.

So I missed the next three meetings for one reason, often because the dates were changed so many times that rescheduling of my affairs was impossible.

On June 20, 1974, I attended a meeting to discuss dilatin for cardiac arrythmias. That is irregular heartbeat.

Park & Davis presented its support for this use, bringing in three of its investigators and some of them revealed their approval of the drug to Park & Davis by making a sign, acknowledged friendship, by similar signs, and revealed their own use of the drug for this nonapproved purpose.

We were told at that meeting by an FDA official, and I found out yesterday it was Dr. Carmen Rosenstein, that the material that was sent to us by the drug company was confidential. We must not reveal it to anybody.

I said, but, that is all published. I wonder what there would be about that that we could not reveal? I really mean your opinions of the published work should not be revealed.

Yet this was even contradictory to our April 13 meeting, when Dr. Belton told us at the end of the meeting, when we had just reviewed propanolol, that he thought we would be getting some votes from the pink sheet and what should he tell the pink sheet?

So I think that whatever decisions are made about our behavior and our understanding, our opinions of this published work should be consistent. We should know exactly what we are supposed to do and I am sure we are going to do it.

But, you see, if some people are going to talk and some people are not, then I think the meeting should be open at all times. Certainly friends of investigators or users themselves should be excluded as advisers, and I think we ought, in order to prevent unsupervised use of drugs for nonapproved uses, that preapproval publication must be prohibited.

You have to get approval for publication of the results of any investigations on drugs for nonapproved uses.

Unless we can tell patients that they should ask their physicians before they get a drug, what are you protecting me from, how carefully have you read the data?

One of the things that happened at lunchtime, there were offiicals of Park & Davis who motioned to me to come over and sit with them at lunch and they said to me, I hear this is your last meeting, your last—the last time you will be meeting with this advisory committee. I took that as something of a threat since it was not at all true, as far as I knew.

Again, we found that Park & Davis misrepresented some of their data by saying that when they had tested dilatin for efficacy in altering atrio-ventricular conduction, they said they had done it in sick patients and actually the work had been done on healthy volunteer prisoners and the mechanism of producing changes in this time were not relevant to what was happening to sick people.

Each year of my service I have filled out a conflict of interest form revealing that I have no interest in drug companies, and no other attachment that would prevent me from participating as a scientist.

I have no personal contact with physicians who perform these investigations and that is largely because I am a woman and that, these contacts therefore could not prevent me from being openly critical if I thought it was necessary.

In fact, I do think that it is important that we have people on these advisory committees who are self-assured enough so that they do not necessarily fall within the in-group. We should be able to take some disapproval of our colleagues and say what is on our minds. One of the reasons that I have been able to do this is that I know that I am out of that group anyway.

On the times that we have meetings two days in a row, we naturally stay over for dinner and I do not get invited to dinner, although it looks to me as though all the other people do have dinner together.

I have—I also do not use drugs for nonapproved uses. I also take it that FDA needed my best scientific judgment on experimental data presented to me. I cannot review data or studies for legalities, but I do my best to review all material as an open-minded conscientious scientist. As such, I have no objection to open transcripts at our meetings and the meetings themselves being open to public attendance.

My experience thus far forces me to conclude that it would be advisable for a patient to ask his or her physician if a drug or drug delivering device that was being prescribed was approved by the FDA and even if approved, if the physician has carefully reviewed all evidence for safety and efficacy personally.

I feel that there has been some pressure put on me, some uncomfortableness because I often have opinions that are not exactly what the FDA might have liked, although I feel that I have been influential with the other members of my committee by presenting data that they could not refute.

However, when we have had meetings, and they have needed an added chairman, and I have been the senior member of the committee present, I was not made the chairman for that particular meeting.

Senator KENNEDY. Thank you very much, Doctor.

You worked on Cyclert, hexobendine and dilatin; you heard the testimony that we heard this morning on those drugs. Has that been consistent with your knowledge of the facts?

Dr. APTER. Yes, entirely consistent.

Senator KENNEDY. I think one of the obvious conclusions that you draw listening to your experience, is that we find medical officers being harassed, being transferred, their reports distorted, altered, changed, cut-off from files, and then we find that the advisory committee which the FDA is relying upon, has almost the same kind of problems as the medical officer reviewing scientific studies.

It appears that the one underlying theme of this is that it only happens when the decisions are being made adversely to the drug companies. I think it is a shocking discovery for all of us.

Doctor?

Dr. FREEMAN. Could I make one additional brief comment?

I know physicians are not supposed to try to analyze situations where they have not seen patients.

However, I have seen enough of the situation to wonder whether part of the complaint of the drug industry is not justified in the sense that when you have a system that operates like this, there is going to be a great deal of insufficiency and procrastination and the decision-making process could be changed, the drug company or the investigators would know in a more rapid or forthright fashion whether, in fact, they had to go back and do more work, or whether they did not.

I think the present system allows for a great deal of uncertainty, even on their part, as to whether they can get by by exerting pressure or whether they will not. I think the question of the drug lag which you raised could be modified if the situation were tightened up.

Additionally, the harassment, the unpleasantness that you have heard leads people into polarized positions so that both the medical officers and some of us, for example, are put in positions where we end up doing or saying things that may look too passionate, too emotional, and then can be discounted by the people concerned. That is also part of this system. Thank you.

Senator KENNEDY. We are going to review this whole procedure in these next weeks and months. This testimony has been enormously helpful and valuable to us, and I want to thank you for your fine and candid statements.

Yes, Doctor?

Dr. APTER. I want to take Dr. Freeman's position one step further.

I think if we had carefully written protocols and carefully annotated investigative procedures set up from the very beginning, that would greatly shorten this so-called lag.

A lot of this lag is because the experiments are done poorly in the beginning.

[The prepared statement of Dr. Apter follows:]

STATEMENT

OF

JULIA T. APTER, M.D., PH. D.

PROFESSOR OF SURGERY

RUSH MEDICAL COLLEGE

CHICAGO, ILLINOIS

AUGUST 15, 1974

ABBREVIATED CURRICULUM VITAE, JULIA T. APTER, M.D., PH.D.

EDUCATION:
University of Pennsylvania, B.A., Physics, 1939.
Johns HopkinsUniversity School of Medicine, M.D., 1943.
Northwestern University Graduate School, M.S., Physiology, 1959.
University of Chicago, Ph.D., Mathematical Biology, 1964.

MEDICAL LICENSES:
Maryland, Illinois, Indiana

CLINICAL EXPERIENCE:
Rotating Internship, Baltimore City Hospital, 1943.
Resident in Ophthalmology, University of Chicago Clinics, 1950-1952.
Attending Ophthalmologist, Whiting Clinic, 1953-1956.
Attending Ophthalmologist, Woodlawn Hospital, 1953-1956.
Attending Ophthalmologist, Mary Thompson Hospital, 1955-1959.
Associate Attending Surgeon, Presbyterian-St. Luke's Hospital, 1966.
Attending Surgeon, Presbyterian-St. Luke's Hospital, 1967-

ACADEMIC AND PROFESSIONAL EXPERIENCE:
Instructor Ophthalmology, Johns Hopkins University, 1943-1946.
Director Laboratory of Neurophysiology, Manteno State Hospital, 1951-1956.
Assistant, Instructor, Associate in Ophthalmology, Northwestern University, 1953-1959.
Trainee in Mathematical Biology, University of Chicago, 1961 - 1964.
Special Fellow of National Heart Institute, 1965.
Research Associate Mathematical Biology, University of Chicago, 1965-1966.
Research Associate (Associate Professor) Surgery, University of Chicago, 1966.
Associate Professor of Surgery, University of Illinois, 1966-1968.
Professor of Surgery, University of Illinois, 1968-1971.
Professor of Surgery, Rush Medical College, 1971-to present
Director, Section of Mathematical Biology, Presbyterian-St. Luke's Hospital, 1966-1971.
Director Laboratory of Biomaterials and Biomechanics, Rush Medical Center, 1971-to present

HONORS:
Honors in Physics, University of Pennsylvania, 1939.
Phi Beta Kappa, 1938.
Sigma Xi, 1940.
Honorary Citizen of Brussels, 1968.
Fellow Academy of Ophthalmology, 1957.
Chairperson of Gordon Conference in Biomathematics, 1969.
Associate Editor,Computers in Biology and Medicine, 1971- to present

BOARD CERTIFICATION:
Ophthalmology, 1959.

NATIONAL PROFESSIONAL SOCIETIES OFFICES HELD:
Institute of Electrical and Electronics Engineers:
Outstanding Speaker, 1973 (Special Competence: Medical Data Analysis) to present
Chairperson of Committee on Medical Engineering Training, 1970- to present
Chairperson of Committee on Professional Opportunities for Women, 1970- to present
Administrative Committee on Engineering in Biology and Medicine, 1969-1975
Biophysical Society:
Director of Placement Service, 1969 to present
Chairperson of Ad Hoc Committee on Education, 1971.
American Association for the Advancement of Science:
Nominating Committee for Medical Sciences, 1974.
American Association of University Professors:
Chapter President, 1973-1974.
Federation of American Societies for Experimental Biology:
Chairperson, Steering Committee for Conference, 1973-1974
Member, FDA Cardiovascular and Renal Disorders Advisory Committee 1972-1976

Senator Kennedy, and members of the Senate Subcommittee on Health, I am Julia Apter appearing upon your subpoena. I wish to summarize my service for the Food and Drug Administration (FDA), my understanding of the role I have played in that service, and my understanding of the role that would be proper for me as a science advisor.

I was appointed a member of the FDA Cardiovascular and Renal Disorders Advisory Committee to serve from July, 1972 to July 1976. I accepted the position since I was under the impression that the FDA protects consumers by preventing the release to the market of drugs that might be harmful to them either because of innate toxicity or because they might be used to heal particular diseases they were not effective for. I was also under the impression that the FDA protects the interests of physicians by supplying them with reliable and complete information about the safety and efficacy of drugs and by preventing physicians from using such drugs inappropriately.

At the first two committee meetings I attended, on September 8 and November 29, 1972, the Committee helped write guidelines for protocols for testing effectiveness and safety of drugs for particular clinical uses. The guidelines we developed strengthened my pre-employment impressions of the functions of the FDA.

By the time of our third meeting on February 14, 1973, I had responded to invitations from two medical officers of the FDA to help other Advisory Committees by reviewing IND data on cylert and hexobendine. I found the investigations on those two drugs had deviated from protocols for testing safety and efficacy. What is more, the investigators had published their findings either as though they had followed protocols or as though the FDA had approved their studies; with a drug-company-employed psychologist, not licensed to practice medicine, even recommending drugs publicly for clinical use. These experiences convinced me that supervision of investigations

conducted by drug companies is needed to enforce adherence to protocols throughout the investigations and to prevent publication before FDA review of the results. Such supervision would: 1) prevent use of investigative new drugs for clinical use before FDA approval; 2) result in more reliable evaluation at the end of investigation; and, most importantly, 3) would prevent risks to patients in improperly conducted clinical trials. These dangers were not averted in the case of these two drugs partly because European studies had been assumed adequate support for clinical use. My studies on cylert and hexobendine convinced me that the USA must conduct its own studies of efficacy and safety before releasing drugs for use by USA citizens since hexobendine, although allegedly effective for some cardiovascular diseases in Europe, proved ineffective here and because European standards for establishing safety are much less stringent than the FDA currently requires. Hexobendine, for example, was used on humans in Europe after tests on only three dogs.

At the meeting on February 14 and 15, 1973, in the Oxford Room of the St. Francis Hotel in San Francisco, though I attended at great personal sacrifice endured only because I was assigned to give my report on the ocular toxicity of hexobendine, the meeting was treated casually in that no transcript was kept and then was cancelled because I insisted on a transcript in compliance with PL 92-463. The Chairman and the Executive Secretary made me feel that they considered my position reprehensible although other advisors did not object. This experience convinced me that all FDA staff employees must be kept up-to-date concerning FDA-related legislation and must act in compliance with it. What is more, advisors who insist on compliance with laws should be treated courteously.

In preparation for the meeting of April 13, 1973, I received about 700 pages of reprints and manuscripts concerning propanolol in the treatment of angina pectoris from Ayerst Corporation, the drug company promoting this use. Thirty-three reprints had been labeled by Ayerst as "controlled studies"; I reviewed these immediately.

Later I was assigned reprints 1 - 12 of the group of 33 for my particular review at the coming meeting. All but one of the 33 were from the published literature. My assignment was to consider 1) Does the study qualify as adequate and well controlled? 2) What efficacy in angina pectoris is demonstrated? 3) Is there concern for safety? I have already testified publically before the Intergovernmental Relations Subcommittee of the House Committee on Government Operations that I found none of those studies qualified as adequate and well-controlled for showing efficacy in angina pectoris and many gave me concern for safety since some patients with angina pectoris were clearly made much worse by propanolol in that their withdrawal symptoms were very severe, even fatal. This experience convinced me that raw data from actual investigative new drug and new drug application investigation must be available to advisors if they are to evaluate drugs properly. It also drew my attention to the fact that investigators were exposing hundreds of patients to risks associated with a drug even though dangers of such exposure was specifically pointed out in the published literature. Therefore there must be tighter controls on such use of drugs in clinical trials by non-supervised investigations of all kinds. It also convinced me that there should be more than one statistician on every advisory committee and more than one person not using the drug for non-approved uses and knowledgeable about clinical and laboratory investigative procedures. I also feel that the FDA officials ought to keep everyone involved alerted to the difference between testimonial presentation and actual data presentation. And I cannot stress too strongly that I feel that publication of investigations should be withheld until FDA review in order to prevent widespread use of a drug which the FDA would then have to curtail or supervise even more widely.

On May 8, 1973 I attended a meeting of the FDA Ophthalmic Drug Advisory Committee to report on my evaluation of hexobendine and its apparent tendency to induce cataracts in humans, as in dogs. I recommended a need for further follow-up of

the patients used in the clinical trial since patients already examined twice (double-blindly) were reportedly having a high incidence of "possibly drug related cataracts". Two advisors of that committee expressed opinions similar to mine. This experience convinced me that "voting" in a group is not the best way to reach the most valid evaluation of a drug unless the advisory group has at least two statisticians and two scientists knowledgeable in the basics of scientific investigation and that no members be physicians using drugs for non-approved uses. The experience also convinced me that industry supported investigators be selected so that they have adequate time to examine patients thoroughly before recording their evaluations and that they be held accountable for the records that they keep, since the physician who found the cataracts said his findings were unreliable because he had been tired and busy when he made the examinations.

At the meeting of September 20 and 21st in Washington we discussed the atropen which would automatically inject atropine into patients having signs of impending coronary occlusion. The discussion made in closed session convinced me that the FDA medical officers should be permitted to contribute more actively to the advisory committee meetings and that the FDA should continually remind the advisors that drugs or instruments not yet proved safe in experimental conditions should not be released for clinical trials. This meeting and others made it clear to me that the FDA was not strictly enforcing the regulation that drugs must be either proved safe in animals or the range of safety must be established in animals before it can be released for any kind of clinical trial. This is essential if only to make it possible to give an honest evaluation of risk to the patient acquiescing to be used in a clinical trial.

On November 30th I received a latter asking me whether I'd be willing to participate in the review of IND's and NDA's by the FDA staff even though that would mean that

I must have a lockable file cabinet in my office and must not reveal any trade secrets. I acquiesced readily but have never been used for that purpose. I missed the meetings of December 6, 1973, February 28, 1974 and April 19, 1974, often because the dates were changed so many times that rescheduling of my affairs was impossible.

On June 20, 1974 I attended a meeting to discuss dilantin for cardiac arrythmias. Parke and Davis presented its support for this use bringing three of its investigators. I noticed some advisors 1) Revealing their approval of the drug to Parke and Davis, 2) Acknowledging friendship for the investigators and 3) Revealing their own use of the drug for this non-approved purpose. Yet we were told by an FDA official not to reveal our opinions even of published work on this drug. This experience convinced me that all meetings should be opened at all times; that friends of investigators or users themselves should be excluded as advisors and, in order to prevent unsupervised use of drugs for non-approved uses, that preapproval publication must be prohibited. It also convinced me that drug companies must be closely supervised for accuracy of reprints since Parke and Davis told us that they had tested dilantin for efficacy in altering atrio-ventricular conduction time in sick patients when the studies had really been done on healthy volunteer prisoners.

Each year of my service I have filled out a conflict of interest form revealing that I have no interest in drug companies and no other attachments that would prevent me from participating as a scientist. I have no personal contacts with physicians who perform these investigations that would prevent me from being openly critical if I thought it was necessary. I do not use drugs for non-approved purposes.

I have always taken for granted that the FDA most needed my best scientific judgement and my most conscientious review of clinical and experimental data presented to me. I cannot review data or studies for legalities, but I do my best to review all material

as an open-minded, conscientious scientist. As such, I have no objection to making transcripts of our meetings and the meetings, themselves, open to public perusal. My experience thus far forces me to conclude that it would be advisable for each patient to ask his or her physician if a drug or drug-delivering device being prescribed was approved by the FDA and if the physician has carefully reviewed the evidence for safety and efficacy personnally.

Senator KENNEDY. I wish to thank all who participated today. The subcommittee stands in recess until tomorrow morning.

[Whereupon, at 1:38 p.m., the subcommittee was recessed, to reconvene at 10 a.m., Friday, August 16, 1974.]

EXAMINATION OF THE PHARMACEUTICAL INDUSTRY, 1973–74

FRIDAY, AUGUST 16, 1974

U.S. SENATE,
SUBCOMMITTEE ON HEALTH OF THE
COMMITTEE ON LABOR AND PUBLIC WELFARE,
AND THE SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE
AND PROCEDURE OF THE COMMITTEE ON THE JUDICIARY,
Washington, D.C.

The subcommittees met, pursuant to recess, at 10:10 a.m., in room 4232, Dirksen Senate Office Building, Senator Edward M. Kennedy (chairman of the subcommittees), presiding.

Present: Senators Kennedy, Nelson, and Thurmond.

OPENING STATEMENT OF SENATOR KENNEDY

Senator KENNEDY. The subcommittees will come to order. Yesterday these subcommittees received startling, alarming testimony from 14 health professionals, all of whom are deeply concerned that the Food and Drug Administration is not fulfilling its extraordinarily important mission of assuring the safety and effectiveness of our Nation's drug supply.

Ten of these witnesses are current employees of the FDA. One has only recently left to join the Social Security Administration. All eleven told the same dramatic story:

That their recommendations to approve new drugs have never been questioned, but their recommendations to disapprove drugs were almost always questioned.

That their efforts to disapprove drugs resulted in repeated harassment from FDA officials—that files were altered and modified.

That industry pressure apparently influenced the drug review process.

That they were all, at one time or another, removed from the review process after recommending disapproval.

That they were all transferred out of their divisions, pursuant to efforts to get specific drugs disapproved.

We heard that the Cardio-Pulmonary-Renal Division was reorganized; several of its members were transferred—usually outside their expertise.

A psychiatrist was ordered to review soft contact lenses. A surgeon was removed from the surgical division to review radiopaque dyes; a cardiologist was removed from the review of heart drugs.

The testimony of all these witnesses was strikingly similar and very disheartening.

The thrust of their testimony was corroborated by the second panel of witnesses—three outside, university-based distinguished FDA Ad-

visory group members. They too told of harassment, official misrepresentation of advisory committee actions, and the difficulty of getting drugs disapproved.

These are very serious charges. They were made in sworn testimony. They cast grave doubts on the ability of the FDA to perform its crucial regulatory activities. They depict a closed system of drug review, with little or no public accountability or input.

These subcommittees intend to investigate these charges. We intend to open up the system to the light of public scrutiny. We are hopeful that today, Commissioner Schmidt will respond to what we have heard.

We have no intention to stifle drug research in the United States. No one wants to see breakthroughs in cancer chemotherapy more than I do. But we also have no intention of letting the public health and safety be put at risk; we have no intention of having a system where dedicated civil servants are harassed by their superiors; we have no intention of allowing distinguished outside consultants to be discouraged from further public service because of shoddy treatment.

I believe this country can remain preeminent in drug research and protect the health and safety of the American people. I believe we can attract top health professionals to Government and encourage them in their efforts. I believe we can open up the processes of the FDA—and I believe we will.

Today we will not only get a response to the charges of yesterday, but will also focus on the question of whether there is a drug lag in the United States.

I recently wrote 20 major drug companies and asked them to list drug products they sold overseas but not in the United States. Eighteen companies responded and listed a total of 336 drug products. I am asking the FDA to study the list and let us know how many of these drugs have counterparts in this country and how many represent significant advances over what is available here.

Twelve of these companies responded, in addition, that they felt this country has a significant drug lag. Three companies said they were not sure, and one said that there is no lag.

We will look closely at this question in the months ahead.

[The information referred to and subsequently supplied for the record, follows:]

THE FOOD AND DRUG ADMINISTRATION

ANALYSIS OF LIST OF 336 DRUGS

TABLE 1

Attached is the list, as submitted by Senator Kennedy, of drugs specified by 16 firms as marketed abroad and not in the United States. This list is the basis for Table 2; the numbers beside each drug refer to the corresponding columns of Table 2 and indicate the manner in which the drug was characterized by FDA.

Many of the trade names provided are foreign ones and/or were misspelled. This created problems in identification, and therefore certain assumptions had to be made. Where drugs could not be identified from the trade name provided, the spelling or other nomenclature which provided the basis for characterization are specified.

Characterizations were based on information generally available, and it is acknowledged that some may possibly be in error (this is especially likely with discontinuations of drugs (#4), so that the figures presented here and in Table 2, Column 4 should be considered minimal). Nevertheless, this represents a serious effort to provide information as accurate and useful as possible from the limited, sometimes confusing, data provided, and using the information sources that are available to any who may desire to conduct similar investigations. It is also acknowledged that firms may have had in mind new (unapproved) uses or different formulations for the U.S., but this information was not provided. The headings and footnotes of Table 2 indicate the basis for treatment of the data.

COMPANY	DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Upjohn	*1 Depo-Provera as an injectible contraceptive	Yes
	*1 Prostin FZA for labor induction	
	*1 Solu-Medrol for immunosuppression in terminal cancer	
	1 Motrin (ibuprofafil)	
	5 Prostin E 2 (dinoprostone)	
Parke-Davis	5 Arlef-Flufenamic Acid	No Answer
	5 Buscopan-N butylscopolammonium	
	5 Poltyn-benzilonium bromide	
Syntex	NONE	Yes
Abbott	1 Dayamin Inj.	Yes
	5 Zumaril	
	1 Dethyrona	
	1 Ethrane	
	3 Bilsan	
	3 Kaltin	
	3 Kaltin w/Neomycin	
	1 Erytrameb	
	1 Theograd	
	Brospamin Appears to not be marketed at all	
	1,4 Bejectal w/Liver Inj.	
	1,4 Bejectal C w/Liver Inj.	
	2 Bevidox Inj	
	3 Bejectal-T Inj. Becjectal Injection	
	1 Thiamine	
	2 Butyn-Metaphen Opth.	
	1 Ioquin	
	2 Erythrocin Opth. Oint.	
	2 Erythrocin Ointment	
	3 Erythrocin-Neomycin Oint.	
	3 Erythrocin HC Oint.	
	1,4 Desbutal	
	3 Torfan-H	
	1 Torfan	
	1 Cobenzil Gradumet Cobenzil Gradumet	
	1,4 Glucophylline	

* Specified for new indications; indications were not specified for other drugs or by other firms.

2902

COMPANY	DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Abbott (Con't)	4,1 Di-Paralene	
	1 Picrotoxin .03% Inj.	
	1 Adrenalin Tartaric Acid Inj.	
	1 Morphine-Atropine Inj.	
	1 Phenobarbital Sod. Inj.	
	1 Papaverine HCL Inj.	
	1 Aminophylline Inj.	
	1 Bromophalein Inj.	
	1 Calcium Chloride	
	4,1 Fenofan	
	4,1 A-C Troches	
	1 Kavitan	
	1 Histamine Diphosphate	
	4,1 Carciovital Inj.	
	1 Prophylthiouracil	
	4,1 Rutin and Ascorbic Acid	
	1 Gerolan	
	1 Motilyn	
	1 Ancyte	
	3 Trividox-Isoniazid	
	3 Digestant Effervescent	
	1 Docevit Docivit	
	2 Adsorl	
	1 Riboflavin	
	4,1 Nembudeine	
	3 Barbico	
	1 Atropine Inj.	
	1 Lignocaine Inj.	
	3 Lignocaine w/Adrenalin	
	1 Procaine HCI	
	1,4 Sulfathiazole	
	Sulfedexan Appears not to be marketed at all	
	1 Streptomycin	
	1 Bacitracin	
	3 Co-Mycine Co-mycin	
	1,4 Compocillin-VK w/Sulfa	
	1,4 Erthrocin-Sulfa	
	1,4 Erythrocin-Sulfa Grans.	
	2 Erythrocin Suspension	

COMPANY	DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Abbott (Con't)	5 Syngomycin Grans Synerg-omycin 5 Arsiven 3 Siden Ciden	
Lilly	1,4 Anhydron KR (Cylothiazide with KCl_4 and reserpine) 3 Co-Elorine 2 Cordran AF 3 Darvon-N Compound 1 Direma 3 Disfalgesic Distalgesic 1 Distamine 3 Doloxene Compound 3 Doloxytal 1 En-Cebrin 1 Ilosone 5 Nalfon 5 Nebcin 3,4 Quintess N 1,4 Sandril w/Pyronil 3 Soluvore 1,4 Topocide 1,4 V-Cillin K Sulpha 5 Vortel	Yes
Merrell	Not Answered	Yes
Searle	5 Aldazina ,Aldazide Aldazida 3 Aldactazine 3 Aldactide 2 Demulen 5 mg. 5 Raudazida 5 Aldatense 5 Solductone 2 Metrulen, Metrulene 2 Ovulen Forte 1 Minigue Miniquen 1 Luto-Metrodrol Luto-Metrodrol 2 Ovulen-Mite	Yes

COMPANY	DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Searle (Con't)	1 Femulen	
	2 Ferrulen, Ovulen FE Ferulen, Ovulen FE	
	3 Lomotil with Neomycin	
	3 Lomomycin	
	1,4 Hydryllin, Neumofluiden	
	3 Dramasina	
	3 Dramacaf	
	1 Darfalan, Darfal Dartalan or Dartal	
	3,4 Nilevar, Solevar	
	3 Anatrophil	
	5 Anabiol	
Ciba-Geigy	5 Adelphane	Yes
	1,4 Adelphane-Esidrix	
	1,4 Adephane-Esidrix-K	
	5 Aldocarten	
	5 Ambilhar	
	5 Anacyclin	
	1,4 Antistine	
	1,4 Antistine-Privine	
	5 Aturbane	
	3 Bradex-Vioform	
	1,4 Bradosol Lozenges	
	Cartantren Unidentified	
	3 Celospor	
	5 Ciba-1906	
	3,4 Cibalgin	
	1,4 Cibazol	
	3 Coromine-Adenosine	
	3 Coramine-Ephedrine	
	3 Ceramine-Glucose	
	1 Cortisone Ciba	
	2 Dianabol Cream	
	3 Dianavit	
	1 Doriden	
	1,4 Elkosin	
	1,4 Entero-Vioform	
	5 Entobex	

COMPANY		DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Ciba-Geigy (Con't)	1,4	Esidrix-K	
	2	Eticyclin Forte	
	2	Femandren	
	3	Gly-Coramine	
	5	Glyvenol	
	1	Hypertensin Ciba	Hypertensin CIBA
	5	Ismelin-Navidrex	
	5	Lioresal	
	2	Locorten Foam	
	2	Locorten Tar	
	3	Locorten-Vioform	
	1	Locasalen	
	5	Ludiomil	
	1	Lutocyclin	
	2	Lut-Ovocyclin Forte	
	3,4	Mexaform	
	3,4	Mexase	
	5	Navidrex	
	5	Nepresol	
	3,4	Nimarol	
	5	Noracyclin 22	
	1	Orisul	
	3	Otricorten	
	2	Ovocyclin	
	2	Ovocyclin Depot	
	1	Perancilen	
	2	Peristaltin	
	3,4	Plimasine	
	5	Procto-Glyvenol	
	1	Resyl/Resyl Plus	
	3	Sistocyclin	
	5	Sistometril	Sistomotril
	3,4	Spasmo-Cibalgin	
	3,4	Spasmo-Cibalgin Composition	
	1	Sycacthen	
	2	Synacthen Depot	
	5	Tacitin	
	5	Trafuril	

COMPANY	DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Ciba-Geigy (Con't)	2 Triolandren	
	1 Ultandren Ultandren	
	2 Ultra-Corten/Ultracorten-H	
	2 Ultra Corten-H Water Soluble	
	2 Ultra Cortenol	
	2 Ultra Cortenol-Vioform	
	3 Yermonil Yermonil	
	5 Anafranil	
	1 Butazolidin Cream	
	3 Delta-Butazolidin	
	5 Dosulfin	
	1,4 Eurax-Hydrocortisone	
	5 Gubernal	
	1,4 Gyno-Sterosan	
	5 Hemexan	
	1 Hygroton Hygroton	
	1 Hygrotan-Reserpine Hygroton-Reserpine	
	5 Indolitan Indolitan	
	5 Insidon	
	3,4 Irgapyrin	
	5 Lamprene	
	1 Medomin	
	5 Micoren	
	1 Pertofrane	
	3 Realin	
	3 Resoferon	
	1,4 Siogen	
	1,4 Siosteran	
	1,4 Sterosan	
	1,4 Sterosan-Hydrocortisone	
	1 Symmetrel	
	5 Synopen	
	2 Tandearil Cream Tan Dearil Cream	
	1 Tromexan	
	Thrombokinase Geigy Apparently not a drug for human use	

COMPANY	DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Squibb	1 Velosef (cephradine) Cephradine 5 Halog (halcinonide) 5 Dexacillin (epicillin) 5 Flaminon (niflumic Acid) 3 Motival (fluphenazine-nortriptylene)	Yes
Burroughs Wellcome	None	Not Clear
Hoffman La Roche	None	No
Bristol-Myers	Not Given	Yes
Johnson & Johnson	3 Ad-Vitan 3 Antichloric 1 Becovitan 1 Benavit 2 Biactone 5 Bilagol 3 Bilamin-Cholin 3 Bilamin-Cilag Bilamin-Cilag 5 Burgochin Burgodin 3 Carbo-Guanicil 5 Ciloprn Ciloprin 1 Cistobil 5 Clinium 1 Clistin Expectorant 2 Clistin-D Elixir 3 Combicilline 3 Daktacort 3 Dicastrepton 1500 1 Digitoxine-Janssen 5 Dimitronal 5 Dipidolar/Dipiperon 1 Egacen-Duriles 1 Endoxan 5 Frenactil 3 Gumox 3 Gumox-N	Yes

COMPANY	DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Johnson & Johnson (Con't)	1 Grifulvin MC	
	5 Haloanisone	
	3 Hematone	
	2 Ifonvan	
	3 Ilan	
	5 Imap	
	5 Imodium	
	1 Jectofer	
	2 Joduron	
	2 Kinidin-Duriles	
	5 Luvatren Luvatren	
	5 Midosal	
	1 Mixobar	
	1 Nalorphine	
	5 Neomeritine	
	2 Opacoron	
	5 Operidine	
	5 Orap	
	1 Orpenic	
	2 Ortho-Novum (.5 mg. nurethindrone .1 mg. mestranol)	NORETHINDRONE
	2 Ortho-Novum (5 mg. norethindrone .075 mg. mestranol)	
	1 Palfium	
	3 Paraflex Plus Forte	
	3 Parafon with Dexamethasone	
	3 Perdolan	
	1 Permease	
	2 Pevaryl	
	Pharongine	
	3 Predniflex	
	1 Propyliodon-Cilag	
	1 Pyridacil	
	3 Rarical	
	3 Rarical with Vitamins	
	3 Resprin	
	2 Retin-A Cream .05%	
	2 Retin-A Liquid .025%	

COMPANY	DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Johnson & Johnson (Con't)	3 Rinomar	
	1 Ronpacon	
	2 Rubalgan	
	5 Semap	
	5 Stugeron	
	1 Sublimaze	
	1 Sulfapyelon	
	Tremblex Apparently not a drug for human use	
	5 Triperidol	
	1 Tropac	
	1 Tylenol with Codine	
	3 Vesalium	
Pfizer Inc.	1,4 Viadril	No Answer
	1,4 Niamid	
	5 Envacar	
	5 Fasigyn	
	5 Minipress	
Merck & Co.	5 Blocadren	Yes
	3 Deca-Indocid	
	1 Duo-Decadron Injection	
	5 Midamor	
	5 Moduretic	
	3 1-6-12 (Vit. B_1--B_6--B_{12})	
	3 Triduralta	
	3 Periactin-Vita	
	5 Pivatil	
	5 Sinemet (Carbidopa and L-Dopa)	
	3 Adju-Fluax	
Smith, Kline & French	5 Cephradine	Not Clear
	5 D-Xylan Polysulfuric Acid	
	5 Epithiazide	
	5 Pyrithioxin	
	5 Mebrophenhydramine	
	5 3,4 Dichloro-methoxybenzyl-penicillin, potassium	
	5 Virginiamycin	

COMPANY		DRUGS MARKETED ABROAD BUT NOT IN THE UNITED STATES	DRUG/LAG
Smith, Kline & French (Con't)	1,4	Sulfaethidole Sulfaethidole	
	1	Prophipendyl Prothipendyl	
	5	Fenoxazoline / Fenozolone	
	3,4	Hydrocortisone, Tyrothricin, Estradiol Benzoate, Sulfathiazole, 2-Aminovaleric Acid	
	5	Virginiamycin, Tetracycline	
	5	Virginiamycin, Polymyxin B, Dexamethasone	
	5	L-Citruline, Acetylaspartic Acid	
	5	Xanthinol Nicotinate, D-Xylan Polysulfuric Acid ~~Polysulfuric Acid~~	
A.H. Robins	5	S-Carboxymethylcysteine	Yes
Norwich Parmacal	2	Adipazin	Not Clear
	3,4	Amebon-Ftalil	
	3	Gastro-Gel with Belladonna Suspension	
	3	Sydolil	
	3	Tripzima	
	2,4	Furoxone Pediatric Suspension	
	2,4	Furacin Lozenges	
	1,4	Furestol Vaginal Suppositories	
	1,4	Isoket and Alphaderm	

SUMMARY: Number of Companies that Answered: 18

ON QUESTION OF DRUG LAG:

Yes	12
No	1
Not Clear	3
No Answer	2

Number of Products Abroad But Not in United States:

Upjohn	2
Parke Davis	3
Syntex	0

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Number of Products Abooad But Not in United States: (Con't)

Abbott	68
Lilly	19
Merrell	No Answer
Searle	23
Ciba-Geigy	99
Squibb	5
Burroughs Wellcome	0
Hoffman La Roche	0
Bristol Myers	No Answer
Johnson & Johnson	75
Pfizer	5
Merck	11
Smith, Kline & French	16
A. H. Robins	1
Norwich	9

TOTAL 336

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TABLE 2 DRUGS MARKETED ABROAD, BUT NOT IN THE U.S.
(From List Supplied by 16 Firms in Response to Inquiry from Senator Kennedy)

Company	Total Drugs Listed	Not * Tabulated	Active Ingredient(s) in U.S.[1] Same 1	Different Form/Use[2] 2	Combination[3] 3	Discontinued or "Ineffective"[4] 4	Contains Molecular Entity Not In U.S. Total 5	Cited as Important[5] Wardell	deHaen	FDA	Having IND/NDA in U.S. Active	Inactive
Upjohn	5		1(4+)	3	0	0	1(4+)	0	1	1(4+)	1	0
Parke-Davis	3		0	0	0	0	3	0	0	0	0	1
Syntex	0	---	-	-	-	-	-	-	-	-	-	-
Abbott	68	2(NM)	44	6	13	14	3	1	0	0	0	2
Lilly	19		8	1	7	5	3	0	0	1	2	1
Searle	23		5	5	8	2	5	0	0	0	0	2
Ciba-Geigy	99	2(U)(ND)	32	16	22	23	28	1	0	2	7	12
Squibb	5		1	0	1	0	3	0	2	0	2	0
Burroughs Wellcome	0	---	-	-	-	-	-	-	-	-	-	-
Hoffman-LaRoche	0	---	-	-	-	-	-	-	-	-	-	-
Johnson & Johnson	74	1(ND)	21	12	21	0	18	0	3	1	6	2
Pfizer	5		2	0	0	2	3	1	0	0	1	2
Merck	11		1	1	4	0	5	2	1	1	3	2
Smith, Kline & French	15		3	0	1	2	11	0	2	0	0	2
A.H. Robins	1		0	0	0		1	0	1	0	0	1
Norwich	9		2	3	4	5	0	-	-	-	-	-
Totals	337	5	120	47	81	53	84	5	18	6	21	27
						TOTAL DIFFERENT ENTITIES[6]:	73	4	14	5	20	22

*Drugs not tabulated were either unidentified (U), apparently not marketed anywhere at present (NM), or are not drugs for human use(ND) insofar as could be determined.

Combinations containing active ingredient(s) discontinued in the U.S. are included in columns 3 and 4.

†Three drugs were specified for new indications; indications were not specified for other drugs or by other firms.

[1]Active molecular entities are, or have been, marketed or marketable in U.S. by this or another manufacturer

[2]Marketed in U.S. as another dose/form/salt/ester/use of same molecular entity.

[3]Active ingredients marketed in U.S.

[4]Known to have been discontinued and/or rated as ineffective in Drug Efficacy Study. Includes drugs from columns 1, 2, & 3.

[5]William Wardell or Paul deHaen or considered by FDA potentially to be significant advances over drug presently available in U.S. See Appendix B of [redacted] testimony for explanation and references, and Table 3 for listing of entities.

[6]Different molecular entities (as opposed to total drugs. Several individual drugs may contain the same principal active ingredient(s). Of the 73 entities, 21 were cited as potentially important; by Wardell (W) only, 3; deHaen (D) only, 12; FDA (F) only, 4; W&D, 1; W&F, 0; D&F, 1; all three, 0.

Table 3 Molecular Entities Not in U.S. (From Table 2, Column 5)

Generic Name	Indication	Potential For Gain*	IND/NDA**		Counterpart (C) or Alternative (A) Drugs
Acediasulfone	antileprotic				C. sulfones, dapsone
Alcofenac	analgestic/anti-inflammatory			I	see Appendix B
Aldosterone	corticosteroid replacement		A		C. mineralocorticoids
Alprenolol	beta-blocker	W,D		I	see Appendix B
Amiloride	diuretic	W		I	see Appendix B
Baclofen	skeletal muscle relaxant	D	A		see Appendix B
Ben(z)peridol	tranquilizer	D		I	see Appendix B
Benzilonium Bromide	anticholinergic				C. several anti-cholinergics A. atropine and derivatives
Benzitramide	narcotic analgesic				A. morphine, meperidine
Benzoctamine	tranquilizer	D		I	see Appendix B
Bolandiol	anabolic/androgen				C. several anabolic androgens
Bromhexin	mucolytic	W		I	see Appendix B
Butylscopolammonium	anticholinergic				C. atropine derivatives
Canrenone	antihypertensive			I	A. many antiphypertensives
S-Carboxmethylcysteine	decongestant	D		I	see Appendix B
Carbidopa	antiparkinson	F	A		see Appendix B
Carbutamide	antidiabetic (oral, sulfonylurea)				C. other sulfonylureas are safer
Chlorindione	anticoagulant				A. heparin and coumarins
Cinnarizine	anti-emetic/vasodilator/ antihistamine, etc.		A		see appendix B
L-Citruline, acetylaspartate	"psychostimulant"				A. antidepressants
Clofazimine	antileprotic/antitubercular		A		see Appendix B
Clomipramine	antidepressant	D	A		see Appendix B
Clorprenaline	bronchodilator			I	A. isoproterenol, metaproterenol, et
Cosyntropin	pituitary hormone, diagnostic	F	A		C. corticotropin
Cyclopenthiazide	diuretic			I	see Appendix B
Dibutamide	"antispasmodic"				C. dibutoline
Dihydralazine	sedative/tranquilizer				C. hydralazine, apresoline
Diisopromine	cholagogue				A. dihydrocholic acid
Dimetholizine	vasodilator/antihistamine				C. several
3,4 Dichloro-methoxybenzyl-penicillin	antibiotic				C. penicillin V
Embramine	antihistamine				C. several antihistamines
Epicillin	antibiotic	D	A		see Appendix B
Epithiazide	diuretic				C. thiazides
Fenoprofen	anti-inflammatory		A		see Appendix B
Fenoxazoline	topical nasal decongestant			I	C. several decongestants
Fluanisone	tranquilizer				C. butyrophenones
Flufenamic acid	anti-inflammatory			I	see Appendix B
Fluspirilene	antipsychotic	F,D	A		see Appendix B

Generic Name	Indication	Potential For Gain*	IND/NDA**	Counterpart (C) or Alternative (A) Drugs
Guanoxan	antihypertensive	W	I	see Appendix B
Halcinonide	topical corticosteroid		A	C. several
Halopyramine	antihistamine			C. several antihistamines
Heparinoid	anticoagulant			C. heparin
Ioperamide	antidiarrheal		A	A. diphenoxylate
Lidoflazine	coronary vasodilator		A	A. nitroglycerin
Lynestrenol	progestin (contraceptive)		I	C. Several. Studied here in combination with mestranol; NDA (1965) non-approvable because of lack of long-term studies to establish safety.
Maprotilene	antidepressant	D	A	see Appendix B
(Medroxyprogesterone)	Depo-Provera (Upjohn) injectable contraceptive +			
(Methylprednisolone Na succinate)	Solu-medrol (Upjohn) immuno-suppression in terminal cancer patients+			
Methylperidol	tranquilizer			C. haloperidol
Niflumic acid	anti-inflammatory			C. (See flufenamic acid-Appendix B)
Niridazole	antiprotozoal		I	see Appendix B
Opipramol	antidepressant		I	see Appendix B
Penfluridol	tranquilizer			C. haloperidol
Phanquone	amebicide			C. nitronidazole, diiodoquine
Phenglutarimide	anticholinergic/antiparkinson			A. sereral, including L-dopa
Phenoperidine	narcotic analgesic			C. meperidine
Pimozide	antipsychotic	D	A	see Appendix B
Pipamerone	tranquilizer			C. buterophenones
Piritramide	narcotic analgesic		I	see Appendix B
Pivampicillin	antibiotic	D	A	see Appendix B
Prazosin	antihypertensive		A	A. thiazides, guanethidine, apresoline
Prethcamide	respiratory stimulant		I	A. doxapram appears superior
(Prostaglandin F2A)	Prostin F2a (Upjohn) labor induction +			
Prostaglandin E2	oxytocic/contraceptive	F	A	C. prostaglandin F2a
Pyritinol	antidepressant	D		A. antidepressants
Staphylomycin	antibiotic			A. Several antibiotics for gram-positive infections. Not used for humans in U.S., to preserve ability to use in animal feeds by avoiding human sensitization.
Sulfaproxyline	sulfonamide			C. sulfonamides
Thiabutazide	diuretic			C. thiazides
Thiambutosine	antileprotic			see Appendix B

Generic Name	Indication	Potential For Gain *	IND/NDA**	Counterpart (C) or Alternative (A) Drugs
Timolol	beta-blocker		A	see Appendix B
Tinidazole	trichomonicide		I	C. metronidazole. IND terminated (197 because of suspected animal tumorigenicity
Tobramycin	antibiotic	F	A	C. gentamycin
Trafuryl	liniment			A. many
Tribenoside	anti-inflammatory	D	I	see Appendix B
Trifluperidol	antipsychotic		I	see Appendix B
Xanthinol nicotinate	vasodilator	D	I	see Appendix B (Xanthinol niacinate)

* See footnote 5 of Table 1
** A = Active; I = Inactive

\+ New indications for marketed drugs (indications were not specified for other drugs or by other firms).

Senator KENNEDY. Senator Thurmond?

Senator THURMOND. Thank you very much, Mr. Chairman. I think it is indeed fortunate today that we are able to hear the views of Mr. Joseph Stetler, the president of the Pharmaceutical Manufacturers Association, and Dr. Sarett, and Dr. Weiner, as they pertain to the very important question of research and development in the pharmaceutical industry.

Surely this industry is one that America wants to succeed in its efforts, to give mankind better health and longer and more productive lives.

It is vital to America's welfare that drug research be encouraged and expanded. Dr. Sarett and Dr. Weiner are distinguished scientists in their highly technical fields and their views I am certain will be of great value to these subcommittees and Senate as a whole.

I suspect that most Members of Congress and the American people generally do not fully appreciate the important role that this industry has played in fighting and overcoming so many fatal and debilitating diseases. Nevertheless, I am well aware that the battle against disease is far from won. In this regard I feel it is most essential that Congress do what it can to promote scientific breakthroughs in this field, that can mean better and longer lives for all Americans.

It is a pleasure for me, Mr. Stetler, to welcome you and your general counsel, Mr. Bruce Brennan, for your reputations are well known on Capitol Hill. We are interested in the health of the American people. That is our goal. I am sure it is the goal of the Members of the Senate, to get the truth, and to do what we can to promote the health and welfare of mankind. We are glad to have you gentlemen here.

Senator KENNEDY. Senator Nelson?

Senator NELSON. I do not have anything now.

Senator KENNEDY. We want to welcome Mr. Stetler, who is an old friend of this committee and who has been helpful to us in times past.

We welcome you back to the committee this morning.

You are accompanied by Dr. Sarett, president of Merck, Sharp & Dohme Research Laboratories and Murray Weiner, who is vice president of Merrell National Laboratories.

We are looking forward to their testimony. I think all of us look forward to the witnesses. Dr. Sarett of course is universally respected and acclaimed for the extraordinary contributions he has made in a wide variety of different areas. I think all of us, the American people, benefited from the research that has been done in the development of these projects that have been made. We look forward to your comments.

Senator THURMOND. Mr. Chairman, may I say that we are marking up the Defense Appropriations bill this morning, and if you will be kind enough to excuse me after a little bit, I will have to go over there. I want you to know my deep interest in these hearings and I shall be in touch with you and I shall read the record and cooperate in every way I can.

Senator KENNEDY. Mr. Stetler.

STATEMENT OF C. JOSEPH STETLER, PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, ACCOMPANIED BY LEWIS H. SARETT, PH. D., PRESIDENT, MERCK, SHARP & DOHME RESEARCH LABORATORIES; MURRAY WEINER, M.D., VICE PRESIDENT, MERRELL NATIONAL LABORATORIES; AND BRUCE J. BRENNAN, VICE PRESIDENT AND GENERAL COUNSEL, PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Mr. STETLER. Mr. Chairman and members of the committee. We are here this morning in response to your request for the pharamaceutical industry's views concerning the status of drug innovation and approval in this country and possible ways of bettering the present system.

The subject is not new and yet despite the attention paid to it and recent improvements in procedures and performance within the FDA, a problem remains.

The present hearings, in our opinion, provide an excellent opportunity to put the matter into a more balanced perspective from which sound public policy can be determined.

We have prepared a longer statement which we have submitted and which we would appreciate being included in the record of the hearings.

Senator KENNEDY. It will be so printed in the record at the conclusion of your testimony.

Mr. STETLER. As had been stated, I have with me today in addition to Mr. Brennan two men who have had extensive scientific training and experience. Both have worked for many years in the pharmaceutical industry.

With your permission, I would like to turn over to them the burden of our presentation. They both have brief statements and we will be here to answer questions.

I would like first to ask Dr. Lewis Sarett to present his statement.

Dr. SARETT. Thank you. The perspective I bring to this discussion of the discovery and development of new medicines is that of a scientist and research administrator functioning within a major pharmaceutical industry research laboratory.

It is a fact that pharmaceutical research over the past three decades has been demonstrably productive. The medicines that have been discovered or developed in pharmaceutical laboratories have demonstrable value in both social and economic terms.

And there is no evidence and—as far as I know—no responsible opinion that the pharmaceutical industry's research functions can be performed as effectively by other research laboratories focusing on the health sciences.

My concern, as the public policy issues of pharmaceutical research are discussed and debated, is that they be resolved in ways that strengthen our capacity for innovation, thus helping assure that people will benefit from this Nation's comprehensive research effort in the biomedical sciences.

To a degree, accomplishment of this objective is dependent upon the performance of the Food and Drug Administration.

In a larger sense, however, accomplishment of the objective is dependent on the public and professional environment in which both the industry and the FDA function. That environment has been a

rapidly changing one and includes a number of elements that cumulatively impose constraints, some desirable and some undesirable, on the processes of discovery, development, testing, and evaluation of new drugs—processes in which both the industry and the regulatory agency are vitally involved.

Among these elements are rapid progress in science and technology, increasing precision and sensitivity in the methodology of measurement, rapid acceleration of public interest in health, greater public expectation that absolute safety and effectiveness can be achieved, the broadened public scrutiny of professional performance, and growing evidence of the social benefit to be derived from improved medicines properly used.

One consequence of the interplay among these and other elements is that both the cost of developing a new drug and the time it takes from candidate compound to new product introduction have increased substantially in the United States.

This situation is sometimes referred to as the "lag" in the evolution of new medicines and it has become customary to debate whether industry or regulatory agency is responsible.

Senator KENNEDY. Do you feel there are important drugs being used overseas which are not available in the United States?

Dr. SARETT. I do. I come to that a little later if you like or I can indicate which ones at this point.

Senator KENNEDY. Will you discuss that later if you wish with as much specificity as you can?

Dr. SARETT. All right. I believe both the pharmaceutical industry and the FDA are doing a reasonably good job, within the total contexts in which they operate, to translate advances in science into advances in medicine.

I believe industry and the FDA have common goals in many respects, and certainly in more respects than would be suggested by much of the current dialog. And I believe the route to progress lies in discussion directed toward constructive answers to soluble problems rather than in argumentation directed toward fixing blame.

There was, during the 1960's, a marked slowdown in the rate of introduction of new drugs, accompanied by a market increase in the investment of time and dollars needed for a candidate compound to meet regulatory requirements. Some part of this was due to the added requirements imposed by the 1962 amendments to the Food, Drug and Cosmetic Act.

Some part was due to overzealous interpretation by the FDA of its new statutory authorities. Some part was due to the changing nature of proposed new medicines, which increasingly were designed to deal with chronic disease and therefore required more evidence of safety in long term use.

Some part may have been due to industry performance itself, although it seems unlikely that standards would decline in the face of abundant and persuasive pressures for their advancement.

Senator KENNEDY. Can you tell us in what areas the FDA was overzealous?

Dr. SARETT. The atmosphere at the FDA flowed from the thalidomide catastrophe and it was present in everyone's mind. The concern that the regulatory agency had at that time naturally was for safety.

Senator KENNEDY. As it should be?

Dr. SARETT. As it should be. But the other side of the equation, the benefit to be obtained by patients who did not have available medicines which might in fact be life saving, was not given due weight during that period. It was a question of a belief and a hope that total safety in medicine was possible. Such, as we all know, is not possible.

Senator NELSON. I am puzzled by that statement of the hope of total safety. I have listened to testimony from witnesses covering the last 8 years, 7½ years. Not a single witness before this committee in 7½ years ever argued for the concept of total safety. Who in FDA was arguing for the concept of total safety in drugs in that period?

Dr. SARETT. My point was that there is a benefit to be derived from every drug. There is a risk which is attached to it. It is possible to concentrate on either part of that equation, if you will, either part of the ratio. It has been characterized by many experts in the field who have studied the environment in the United States and in some other countries as being one which emphasizes total safety and deemphasizes the benefits to be derived from the drug.

Senator NELSON. Your generalization is very puzzling to me. In the first place, you are talking about a country that does have a law requiring safety, and you are comparing it with a lot of countries that do not have any law at all.

In Mexico as well as in many other countries, you can buy chloramphenicol over the counter. It is sold and promoted all over the world without any safety guidelines at all. So I would like to have you be a little more precise.

I never heard anybody from Dr. Goddard all the way through Dr. Schmidt, and any of the witnesses from FDA, or any doctor from any place in the country or any pharmacologist—and we have had the most distinguished—ever argue for that concept at all. If they were going to argue that concept, they would take chloramphenicol off the market tomorrow, if that is what they believe.

Dr. SARETT. There are other examples. Rifampin would be a good example, used for tuberculosis. Delay in the approval in this country would allow many patients, who are resistant to other therapies for tuberculosis, to perhaps die. If rifampin has side effects or adverse reactions, which sometimes characterize its effects on patients, it would be possible, indeed likely, for a regulatory agency to dwell upon those and overlook the fact that many patients with tuberculosis were in fact in severe discomfort, and their condition would be deteriorating because of the lack of availability of that drug.

Senator NELSON. Well, of course, tuberculosis rate went down dramatically long before that drug.

Dr. SARETT. Yes, but there still has been a hard core of difficult patients to treat. The numbers are in the thousands. There is still a substantial number. You are perfectly right, the numbers have gone down because of the contributions of the pharmaceutical industry, as you are well aware. Streptomycin has been introduced, and rifampin is, of course, one of the more recent drugs.

Senator NELSON. Your statement still is not very clear to me.

I would like to ask another question. You said at beginning that there has been a substantial drop in the availability of or slowdown in the production of new drugs partly as a consequence of the Kefauver amendments of 1962.

Would you document that?

Dr. SARETT. The phrase that I used was that some part of this was due to the added requirements imposed by the 1962 amendments to the Food, Drug, and Cosmetic Act.

Senator NELSON. Obviously, the Kefauver Act dramatically reduced the number of worthless drugs coming into the market and caused removal of 6,000 of them, because for years—since 1938—the law had only been that all you had to prove was safety. So if you produced a safe drug with nothing in it, you could sell it and lots of them were. Are you talking about useful, valuable entities, which were reduced in number as a consequence of the 1962 amendments? Is that what you are saying?

Dr. SARETT. Yes; I am referring to the fact that there was a marked increase in the investment of time and dollars needed for a candidate compound to meet regulatory requirements.

Senator NELSON. Then I did not understand. I thought you said there was a slowdown in the number of drugs coming into the marketplace in part due to the 1962 amendments. Is that what you said?

Dr. SARETT. That is part of what I said.

Senator NELSON. Let me read this to you, because I read it to Mr. Stetler a year ago at the hearings, and he could not review the statistics, and maybe after a year of thinking about it, you can.

According to a study made by DeHaen, the number of new single entities reached the peak of 63 in 1959—that is the DeHaen study, and that is before the enactment of the Kefauver amendment. The Kefauver amendment was not enforced until 1964. Here are the statistics in Mr. DeHaen's study, which as far as I know, nobody ever attempted to refute: The number of new chemical entities dropped from 63 in 1959 to 45 in 1960, to 41 in 1961, to 28 in 1962, to 18 in 1963.

So now it went from 63 to 18 before the Kefauver Act was enforced.

Then it went to 17 in 1964. Then it jumped to 25 in 1965. So in 1965, the efficacy requirement was in effect, and it went to seven drugs above what it was in 1963 before the act was enforced. Thirteen in 1966. Twenty-five in 1967. Fourteen in 1968. Eleven in 1969. Sixteen in 1970. Fourteen in 1971. Eleven in 1972.

His study did not go beyond that.

So the pattern at least of single entity drugs according to DeHaen apparently did not change at all.

Dr. SARETT. The one you gave was 11 in 1972, and you had larger numbers in earlier years—that is a decrease.

Senator NELSON. Eighteen and nineteen in 1963, and it dropped most dramatically before there was any amendment from 1963, single entity drugs, in 1959 to 18 in 1963.

Then came the 1962 amendments and it went as high as 25 on two occasions after the act.

So I do not see how your argument can be sustained. The statistics just refute you.

If you have some other ones, I would like to see them.

Dr. SARETT. I think you have to look at it in terms of significant drugs which are not available or which have been delayed in their introduction to the United States. I think you have to look at it in terms of the number of pharmaceutical companies that have introduced new drugs.

The number of pharmaceutical companies which were in a position to introduce new drugs in 1963 was something like 89, and that number has dropped to about 30.

Senator NELSON. We had testimony from Dr. Edwards, Dr. Simmons, and Dr. Schmidt, which I have not seen refuted, that there are no significant drug entities in the marketplace anyplace in the world that are not available now in the United States or for which there is not a reasonable substitute available. That is a rough paraphrasing, and I have not seen that refuted.

As you know, you can go into other countries that do not have any standards at all. I have talked to German scientists about it who are appalled by their law. Sure, you can get a drug into the marketplace very easy over there. It may turn out to be a good one. Our law, on the other hand, says you have to have scientifically controlled studies to prove safety and efficacy. Is that not a reasonable standard?

Dr. SARETT. There are requirements for substantial evidence of effectiveness, of course, which were introduced in the 1962 Kefauver-Harris Act. That requirement for substantial evidence for effectiveness was quite detailed, takes time, takes money, takes manpower. In doing so, in providing those elements, it obviously serves to delay the entrance of a drug to the marketplace.

Senator NELSON. Should it not?

Dr. SARETT. That is a matter of interpretation.

Senator NELSON. What are you really saying? You have to prove by adequately controlled, carefully controlled scientific studies that it is safe and efficacious. Are you saying you should not have to make studies? If you do make any studies at all, obviously there will be a delay.

Dr. SARETT. Certainly you are correct. Safety and efficacy must be established. But the determination of what is a satisfactory demonstration of efficacy is a matter of interpretation. Different regulatory agencies interpret that differently. The physicians interpret it differently.

As I understood it the question was: In the United States at any time in the past has the FDA over rigorously interpreted those requirements and I was saying that the FDA at one time—in the 1960's particularly, although (and this is an important point) not so much recently—did very rigorously and very zealously interpret those requirements relative to other regulatory agencies who have had a satisfactory drug record over the years.

Senator KENNEDY. We heard yesterday from various scientists and review and advisory committees to the effect that it was going just the opposite way at the present time. The researchers stated that there was a dual standard. They were being overturned by their superiors, there were alterations in the files, withdrawal of certain material, misrepresentation of scientific data, and false and misleading statements made by the drug companies. Perhaps we ought to be going back to the time where this kind of caution was being exercised by the FDA. That is just a comment and not directed toward your company, but these charges were made before this committee by distinguished scientists and researchers. You certainly would not gather the impression listening to those researchers yesterday that the FDA was being overzealous at this time.

Let us continue.

Dr. SARETT. May I?

Senator KENNEDY. Yes.

Dr. SARETT. But there is evidence that a different picture for new product introductions is beginning to emerge in the 1970's, and there is no reason for optimism.

The presentation here today provides encouraging evidence of the steps that have been taken and are now under consideration to facilitate the evaluation of new drugs.

As I offer in my own brief summary the viewpoints that seem of particular importance, I should state that we have been heartened by the energetic efforts made by the FDA in the last few years to strengthen their performance, and I hope our industry's efforts have been comparably improved.

1. New steps should be taken to assure that FDA and a company sponsoring a new drug reach early agreement on important preclinical and clinical requirements. These should not be arbitrarily changed after costly and time-consuming studies have been launched or completed.

2. The concept of institutional decisions as opposed to one-man decisions, should be reinforced and implemented. The assessment of an NDA is too complex and has too much import for any one individual to decide unilaterally on the drug's merits and limitations.

Senator KENNEDY. Let's discuss point No. 2. The procedures that we heard outlined yesterday indicate that there is extremely elaborate review, not just by an individual, but by consultants, review committees, advisory committees. But let me ask you, as you point out the concept of institutional decisions as opposed to one-man decisions, would you have any reservation about recording the contacts that were made by drug companies with the FDA on particular products?

Dr. SARETT. In general, no. I think that is very healthy. There is confidential material sometimes involved. I think that is a problem. It can hardly be opened to the public.

Senator KENNEDY. That could be maintained confidential. There is obviously a fine line between cooperation and interference, and this is something we are concerned about. But you would not have a problem with the recording of contacts that are made within the various agencies on particular drugs?

Dr. SARETT. Not in general; no.

Senator KENNEDY. Dr. Weiner, could you comment on that?

Dr. WEINER. Well I think that in actual fact there are records kept of just about every meeting. I know that I have never been at a meeting at the FDA—and I have been at quite a few of them — where a specific monitor was not specifically invited to attend along with whomever else attended. In fact I understand it is the policy that minutes are kept of these meetings and should be kept. The minutes are either written by FDA and sent to the company or written by the company and sent to FDA for their comment. It has been my understanding that is FDA policy.

Senator KENNEDY. We heard yesterday to the contrary. But we will let the FDA respond to this. I understand your testimony then that you have absolutely no reservations on any informal contacts that are made with the FDA, having a record kept of them?

Dr. WEINER. No problem at all as long as the material is kept confidential where it is necessary.

Senator KENNEDY. Thank you.

Dr. SARETT. No. 3. It is essential for the FDA to continue to broaden the professional base for its decisionmaking. This begins, of course, with the FDA staff itself—which has the ultimate responsibility for regulatory action, a responsibility that cannot be delegated. But it includes broadening the Agency's use of expert advisers from inside and outside of Government.

4. The FDA's advisers should include experts whose responsibility it is to help the Agency weigh the benefit-to-risk equation. Experts in animal and human pathology, specialists in relevant fields of medicine, and others — with broadened participation and a more formal organizational structure — could serve to lighten the heavy technical and ethical burden which an FDA officer may feel he has been carrying singlehandedly.

5. I applaud both the sequential NDA submission concept and the efforts being made to reduce the deluge of data accompanying an NDA.

6. FDA should also broaden its bases for accepting clinical data from overseas as part of an NDA submission. There are many excellent investigators abroad, and to fail to give their data the same consideration extended to U.S. investigators is to risk delays of years in the introduction of new drugs.

Important though they are, suggestions such as the above deal only with mechanisms. More important is the affirmation of public policy objectives that focus on what is needed to assure progress.

For new and existing medicines to provide optimal benefit, there must be many things—experienced and informed physicians, balanced and effective communication, aware and motivated patients, the existence of an efficiently functioning health care system, and so on.

But new and improved medicines must first exist. Laboratories such as ours have made fundamental contributions of unquestioned social value in our relatively brief life span—in our case, cortisone, streptomycin, probenecid, several of the vitamins (including B–12), chlorothiazide, methyldopa, measles and rubella vaccines, to name a few.

This year my company is investing over $100 million of its earnings in research, much of it very long-term.

Senator KENNEDY. Is that more or less than is invested in advertising, marketing and promotion?

Dr. SARETT. I do not have those figures at hand, I am sorry. I can get them and put them in the record.

About 80 percent of our research is directed to the search for new products, and the rest seeks improvements in existing products.

What do we need to sustain and extend this kind of research endeavor?

First of all, we need recognition. The portrait drawn of industry research in some quarters has a debilitating effect because it contains no acknowledgment that what we do—and what we try to do—has social value.

Second, we need encouragement. We need things that will help our managements have confidence that any success in its unusually high research investments will not be expropriated, although that term would never be used.

Senator KENNEDY. What does that really mean?

Dr. SARETT. That means that the right of the company and its shareholders to receive a fair return must be safeguarded, through the patent system and through the other safeguards we have.

Senator KENNEDY. I do not understand "any success in its unusually high research investments will not be expropriated." Expropriated by who? By other companies? By government?

Dr. SARETT. By any other source. An invention is supposed to be, as you know, an incentive to discovery. Discovery is supposed to be beneficial to society. For a period of 17 years there is a term of protection for that invention and for those who have invested in the development of it. Any move which would tend to undermine or weaken that system would undermine or weaken innovation in the pharmaceutical industry.

Senator KENNEDY. Has it happened in your company? Can you give us some examples of how it happened?

Dr. SARETT. Compulsory licensing, for example, so that an invention was made available immediately to those who had not participated in the discovery or shared in the expense of development—that would be one example of expropriation. We do not have compulsory licensing.

Senator NELSON. I have proposed compulsory licensing under certain conditions such as when the public was being unconscionably exploited. This would be with a reasonable royalty being paid to the manufacturer. If there is a life-saving drug of which the price charged by the company, because it had a patent, was unconscionably high, I for one feel that we ought to have compulsory licensing.

But given the nature of the Congress, you are not threatened much by my bill.

You made reference to threats to the patent, which is supposed to give an invention 17 years protection. I just would like to call attention to the fact that the greatest invention of the drug industry is the trade name which gives you the opportunity to extend the 17-year monopoly far beyond the limitation set by Congress. This is accomplished by trade name identification, trade name prescribing by the doctor, and anti-substitution laws in 44 States. Would you not agree that that ought to be eliminated? Anti-substitution laws, trade name prescribing?

Dr. SARETT. Acting in the opposite direction, of course, is the increase in time for development of new drugs. So that in effect the 17 years of patent protection become shorter all the time. That period of protection is eroding, becoming less because of the great development time that it takes. So that by the time a drug is on the market, there may be only a very few years of patent life yet.

Senator NELSON. I will let you proceed. I do not want to divert to another question.

Dr. SARETT. Finally, we need to have full assurance that when we settle on a new product candidate, and spend millions of dollars and many years in its development and testing, it will be reviewed expeditiously and fairly by the FDA according to previously established standards that reflect sound medical and scientific consensus.

I appreciate your courtesy, Mr. Chairman, and I will do my best to be responsive to any additional questions the committee may have.

Senator KENNEDY. Thank you very much. Perhaps you could review with us my earlier question about what drugs were available overseas that are not available here.

Dr. SARETT. I will be glad to. You will remember my point was that during the 1960's particularly there was a gap in time between introduction and general availability of drugs in sophisticated countries overseas and in the United States. I also said that in recent times that gap is being reduced, so that taken overall then some of the drugs which I think are significant—and I base my opinion I should say incidentally on expert medical judgment, not being a physician myself—would include some which were subsequently approved by the FDA. One of them is cromolyn.

Senator KENNEDY. Could the drugs that are available overseas now that have some special importance or significance, not drugs that in the past were introduced overseas and finally approved here.

Dr. SARETT. Drugs to reduce hypertension—for example, clonidine, and bethanidine—have been available for some time in England. L-asparaginase has been available in Germany since 1969, in France, England and Italy since 1971.

Senator KENNEDY. Are those produced by all European national firms or are any of them being produced by Americans and sold abroad?

Dr. SARETT. L-asparaginase is being produced by a German firm. Clonidine and the other agents——

Dr. WEINER. It is a German firm, but they do have an American branch, and they have had NDA pending for quite some time.

Senator KENNEDY. How long?

Dr. WEINER. I do not know exactly, but it is a question of years.

Senator KENNEDY. Do you have a list of them? Are you giving them off the top of your head?

Dr. SARETT. I do not have them broken down according to which ones are not now available in the FDA.

Senator KENNEDY. For these particular drugs you mentioned, are there counterparts in the United States?

Dr. SARETT. Not precise, no.

Senator KENNEDY. We are not really referring to precise equals. What sort of alternatives are there?

Dr. WEINER. May I comment?

Senator KENNEDY. Yes.

Dr. WEINER. I think if we take the drug we are now speaking about, which is antihypertensive drug, there are quite a few hypertensive drugs. Actually mortality from hypertension has been significantly reduced by these available drugs, and the Government amongst others currently have a campaign to encourage people more quickly to get treated so as to prevent strokes and heart attacks and prolong life. What the experts do say is that the greater the spectrum of mechanisms by which these drugs act, available to them, the more beneficially they can select from amongst these candidates for each patient. While it is certainly true we have ways of treating hypertension, we haven't licked hypertension. I have no doubt that this particular drug which acts in a manner different from all those available would make a significant contribution because we are dealing here with something like

18 million hypertensions in the United States, of which a certain fraction I am sure would benefit from this drug.

Senator KENNEDY. With regard to this drug, you believe that there is no therapeutic equivalent for it available in this country?

Dr. WEINER. Not an absolute equivalent.

Senator KENNEDY. And, secondly, that the range of alternatives is extremely important for any medical official in prescribing a course of therapy for a particular course of therapy?

Dr. WEINER. I do think the range of alternatives is a factor and should be as broad as possible.

Senator KENNEDY. Is the primary area hypertension? What others are there?

Dr. WEINER. There are several other compounds, as you know, there are two which have been available for years, but have just this year become available so that lag is over. They are intal for asthma, which is totally new and different, and alupent also for asthma, which does have an equivalent in the inhalation form, but really does not in the oral tablet form.

The rifampin has been already mentioned for tuberculosis, which I think is a very important and clearly lifesaving drug.

There are beta blockers, which are somewhat equivalent to the propanolol, which you heard about yesterday, which did not have certain pharmacologic components, which may be responsible for some of the undesirable effects of propanolol. An example of that is oxprenolol. Oxprenolol has been available for years overseas and is not available here.

Senator KENNEDY. We are going to supply the committee list to the FDA and ask them to comment on it.

Dr. WEINER. There are others.

Senator KENNEDY. That is all right. Why don't we go ahead.

Dr. WEINER. Mr. Chairman and members of the committee, I am pleased to have the opportunity to add some brief comments on behalf of the pharmaceutical industry on the important subject of drug research and innovation.

It is my impression, that most scientists give too little thought to the need to defend what they consider the self-evident value of medicinal and pharmaceutical research in this modern age of science.

In so doing, they neglect a serious obligation. In my opinion, they must accept greater responsibility to explain to the public how they evaluate the risks of proceeding versus not proceeding with clinical research at a given point. In the last analysis, the people's welfare suffers in direct proportion to the extent to which sound drug research is inhibited.

There has been an understandable regulatory emphasis on reducing the risks of pharmaceutical research. We applaud every measure which makes a real contribution to this goal.

However, in seeking this result, we must not lose sight of the following facts:

1. There is no human endeavor totally free of risk—least of all inaction where innovation is needed to relieve suffering and preserve life. We must strengthen our support for the admirable human quality which has prompted informed volunteers to play a critical role in the development of drugs that save millions from death and misery.

2. Preclinical safety studies, including studies in animals, are never completed. We are still doing experiments and learning important new facts about drugs which have already proved useful over a period of hundreds of years. At each step in the drug research process judgments must be made as to how much and what kind of human exposure to a drug is justified by how much and what kind of preclinical testing.

3. The tremendous variability of problems from drug-to-drug and situation-to-situation makes it impossible to write into law or regulation a definitive description of required tests. Such descriptions intended to cover all drugs are destined to be inappropriate for many or most drugs. Flexibility must be preserved for those scientists most directly involved in the investigation. By and large, they have the greatest knowledge and background experience concerning the particular drug and the conditions of its study.

4. The incontrovertible facts of the relationship between dose and response in every area of safety and efficacy cannot be changed by legislation or regulation. It is a violation of conscience and science to impede drug research on the unfounded assumption that the repeated daily administration of toxic doses of a drug in animals for years is required to make a judgment about the safety of a single small dose of the drug in man.

Senator KENNEDY. Such distinguished individuals as Dr. Rauscher, the head of the cancer agency, would take issue on that, about the ingesting of carcinogenic substances, diethyl stilbestrol and others. This is not a uniform scientific consensus.

Dr. WEINER. I am sure there are always scientific differences of opinion.

Senator KENNEDY. But that is a fairly substantial one.

Dr. WEINER. Yes, but I think that even if you questioned the doctors of the opposing opinion, they would all agree, for example, that we have in our food carcinogens. We walk in the sunlight which is clearly carcinogenic. But everybody recognizes that the dose that we are dealing with is so infinitesimal and unimportant that we just cannot possibly make the fact of carcinogicity in a qualitative sense the sole basis for judging the value of a compound. So if the carcinogicity turns up only as a statistical thing after years of totally unphysiologic doses, I think that is a poor basis on which to condemn what could be a very useful drug or to concern yourself that a single small dose is therefore dangerous.

Senator KENNEDY. That is a value judgment. In many areas there is woeful little research. There are some studies that have been done on carcinogenic substances which would differ with that observation.

While I have you on this point, in your just point you say, "We must strengthen our support for the admirable human quality which has prompted informed volunteers to play a critical role in the development of drugs that save millions from death." That is, I am sure, so.

As we have seen in this committee, the people who have in far too many instances been used have not been informed and in too many instances they have been either prisoners, mentally retarded or poor people.

I think that is a startling fact, which was established over the course of our hearings in the area of human experimentation.

I am sure you want to make sure that the subjects of experimental research are not selected out of particular classes of people, and secondly that everyone is adequately and fully informed, which in far too many instances has not been the case.

Dr. WEINER. I quite agree with you, Senator. I do not know in how many instances it has not been adequate, and I certainly think it should be adequate in each instance.

I think, however, a certain atmosphere of implication is that we go to prisoners because they are prisoners, and that is unfortunately misfounded. One of the major reasons why prisoners are employed and sought as volunteers is because they happen to have the unhappy circumstance, from their point of view, of being very easily observed 24 hours a day, while other volunteers would have to stop their work or eliminate themselves from the usual routine to undergo such close observation.

Senator KENNEDY. Is it cheaper?

Dr. WEINER. By the mere fact that they are available, it is certainly cheaper than if you took a working man and told him stop work and come into an institution 24 hours a day. In that sense, it is.

The key thing is that we would be just as happy to use monasteries, nunaries, any other kind of population, any kind of population which represents a group that is available for continuous observation. That is really the key factor and not whether or not they are prisoners.

Senator KENNEDY. Continue please.

Dr. WEINER. In view of these facts, it is extremely dangerous to the welfare of volunteers and patients to substitute rigid rules for scientific judgment.

We sincerely invite your assistance in our efforts to avoid pointless and costly interference with the potential of science to contribute to the health and comfort of many among us who will surely be stricken in the future by diseases not yet conquered.

Congress should insist that any additional restrictions on the drug research process be of proven value before the interference and diversion they impose are accepted.

We recognize that the regulatory agencies need and deserve the cooperation of the pharmaceutical industry and other interested research scientists. In this spirit we try, with increasing success, I believe, to work with FDA scientists and make recommendations which will aid in the quality and efficiency with which the FDA accomplishes its purposes.

To help achieve our common goals, we would like to see the development of the following concepts:

1. The "closed-end" IND concept which will safely and expeditiously allow the efficient generation of critically important information. In the long run, such information reduces the ultimate degree of risk associated with new drugs.

2. The "sequential NDA", already referred to by Dr. Sarett, which allows each facet of an NDA to be evaluated and accepted as adequate data are generated.

3. The "certified summary" which reduces an NDA to a manageable package which can be reasonably studied, with full data available for spot checking.

4. A scientific appeal process when a forced halt in research or marketing is imposed on the basis of a scientific judgment about which there is a strong difference of responsible opinion.

5. A continuing trend to have important scientific judgments reflect the consensus of the best available experts in the scientific community, as represented by an appropriate committee. The burden of important scientific decisions should be largely or primarily with such committees, rather than with one or a few individuals within the FDA. There should be an obligation to accept the scientific decisions of such expert committees without raising the straw man that such acceptance constitutes an abrogation of FDA's legislated responsibilities.

6. The committee process should assure review by a group representing a full spectrum of expert opinion. To this end, no one organization, including the FDA, should have the sole power of selecting all committee members. A variety of appropriate speciality societies and other learned groups should participate, and no knowledgeable group should be automatically excluded.

Senator NELSON. You suggest the creation of scientific committees composed of the best experts in the various areas involved. That was precisely the process followed in using the National Academy of Sciences-National Research Council for evaluation for the efficacy of drugs under the 1962 amendments over which the drug industry was vociferously upset. But that is precisely what they did. They set up panels on antibiotics, as well as on various therapeutic categories. They were composed of the best experts in the country. They removed large numbers of drugs from the marketplace despite protests from the PMA and the individual company. Almost all fixed combination antibiotics were removed. I think that was a good process.

Dr. WEINER. To the best of my knowledge, we did not disapprove.

Mr. STETLER. We not only did not disapprove, but we worked very effectively in setting them up.

Senator NELSON. But you did oppose the standards.

Mr. STETLER. Individual companies may have had different opinions on different decisions. We never disagreed with the process. We endorsed it then and do now.

Senator NELSON. Some of your members objected to the decisions on antibiotic fixed combinations.

Mr. STETLER. You do not waive your right to dispute a decision just because you agree with the mechanism.

Senator NELSON. You agree with what NAS/NRC did in evaluating drugs?

Mr. STETLER. We agree with the way they did it. Individual disputes occurred. There was no dispute over the mechanism.

Senator NELSON. I am glad to know that. That was not my understanding.

Dr. WEINER. Concern for conflict of interest could be overcome by the diversity of membership, and not by exclusion of those experts whose intense interest and direct experience with drugs makes some contact with their scientific colleagues in industry almost inevitable.

In conclusion, I would like to touch briefly on some of the current discussions concerning the British versus the U.S. system for reviewing drug development.

Starting from the reasonable premise that our scientists are approximately equally skilled, it is fair to ask why the British public has had the advantage of earlier availability of several important drugs, the usefulness of many having been later acknowledged in the form of an approved NDA in the United States.

In many instances, the unavailability of improved drugs does not mean that the population is exposed to fewer dangerous medications but rather that their physicians are obliged to select from a narrower range of less satisfactory medications.

The more quickly better drugs are made available the less likely that the patient will be exposed to the older, less satisfactory drugs or the risks of untreated disease. The current campaigns to find the untreated or inadequately treated hypertensive patient, the diabetic patient, and others, is a reflection of the important role of safe, effective, and ever improving drugs.

The more rapidly we develop effective, improved drugs, the less likely will we be to have harmful effects from either drug or disease. This should be our primary goal.

Thank you, Mr. Chairman, for the opportunity to participate. My colleagues and I will be glad to attempt to answer your questions.

Senator NELSON. Thank you very much. Just a couple of questions. I notice that the House of Delegates of the AMA in June took what struck me as a regrettably long step backward toward bad medical practice when they voted to work for the repeal of the efficacy requirement of the 1962 law.

As I recall, Mr. Stetler, you favored the statute. In your testimony before the monopoly subcommittee, you approved of the efficacy requirement. Do you agree with AMA on this vote?

Mr. STETLER. This may startle you, Senator, but you and I are in complete agreement in our reaction to that action.

Senator NELSON. I must say it will probably ruin both of us that we are on the same side. [Laughter.]

If I understand what you are saying, you agree with the efficacy requirement. Your complaint is that the procedures and processes for evaluating IND's and NDA's is not rapid enough, efficient enough, and when there is a dispute between scientific experts, there is not a good mechanism of utilizing outside qualified committees to resolve the dispute. Is that the essence of what your testimony is?

Dr. WEINER. I would say yes, that is of course a qualitative thing. I think it is better now than it was 5 years ago. But I think there is still lots of room for improvement.

Senator NELSON. I just want to make one point. The argument that you make, that PMA also makes, that there are more drugs on the market in Europe than here may be true. On the other hand, they get many more drugs in the marketplace in Europe—I do not have the list in front of me—but most of the industrialized European countries or a good percentage of them have compulsory licensing requirements. How come it does not discourage innovation there when you are arguing, doctor, that such a thing would hamper development of new drugs. That puzzles me. I do not have the list, but I think France, Germany, Great Britain, Italy——

Dr. WEINER. I am not an expert in that field, and I do not think I would attempt to answer it. I think from what little I know of it, I

would say if the whole world, including the United States, were like Italy there would be precious little pharmaceutical private research done.

Senator NELSON. Pardon me?

Dr. WEINER. If the rules here were like the rules in Italy, I think you would see pharmaceutical research reduced markedly.

Senator NELSON. I regret I cannot rely upon my memory because it is several years back, but I think England, Germany, France, which is the heart of the industrial community of Europe, which you are praising for the number of drugs they have on the market, have compulsory licensing.

Mr. BRENNAN. Senator, while there may be some compulsory licensing provisions in the laws of those countries, those provisions are severely restricted and in fact there is very little use of such provisions.

Senator NELSON. There is a very interesting recent case in which the British Government again I will correct the record and check the statistics—but the British Government required the manufacturer of Valium which is selling in England for about one-third the price it is in the United States, to cut its price by 75 percent, on the grounds the price was exorbitant.

Mr. BRENNAN. That is a price-fixing scheme.

Senator NELSON. That is part of their statute.

Mr. BRENNAN. I do not think that has anything to do with compulsory licensing. That is just a government price-fixing scheme.

Senator NELSON. All right. Just one question for the record. You gave as an example a drug that was available in Europe, valuable entity, and not available here, oxprenolol; is that not correct?

Dr. WEINER. Yes; that is correct.

Senator NELSON. Well, that is for, am I correct, cardiac arrythmia?

Dr. WEINER. Yes.

Senator NELSON. Let me read you the testimony on that and see if you disagree with this. It was testimony a year ago.

The FDA points out, one, that practolol has been associated with the production of cancer in animals; two, that oxprenolol is closely related to it structurally; three, that two committees of experts including experts from the National Cancer Institute have recommended against the present release of these drugs for marketing and have called for further tests to clarify the serious cancer questions; four, that there is a viable alternative to these drugs; and five, that these two drugs are available for emergency purposes in the occasional patient who may not respond to propanolol, which is available.

Are you saying the procedures the FDA followed here that the NIH panel are incorrect, and we ought to put oxprenolol on the market anyway?

Dr. WEINER. I think the opinions you read from that panel are far from unanimous. There are other groups that questioned it. Certainly the concept that the compound is related to one which was found to be carcinogenic in animals, in this case has a double question mark because carcinogenic activity of the original one is only demonstrable, is only evident in certain peculiar strain of animals. With oxprenolol, the carcinogenic studies have been completed and comes out perfectly clean.

On balance, whether there was a justification for continuing to deprive the people who might benefit from this drug, on the basis of this rather narrow extrapolation from one compound to another, I think you will find a lot of scientific difference of opinion.

Senator NELSON. I am puzzled by that. Here we have a scientific group who said that we should not put it on the marketplace until the very serious question of the carcinogenicity is determined. But they also established a policy that makes oxprenolol available to any patient who gets adverse reactions from the available drug which is now in the marketplace. What is wrong with that procedure during the course of further carcinogenicity studies?

Dr. WEINER. I think from the public health point of view that borders on useless. Because the number of people who might well have benefited from oxprenolol over propanolol is much larger than the number that would actually be in a position to go through the procedure you described of making it available through special requests and so forth.

Senator NELSON. The FDA did not specify any particular procedure, except that it was available to be prescribed by a physician in those cases where the patient does not tolerate the drug that is available in this country. What is wrong with those procedures?

Dr. WEINER. I doubt if it is available in any pharmacy that I know of in the United States.

Senator NELSON. Your testimony is that despite strong language of caution about the serious implications of carcinogenicity, if you had the authority, you would overrule it and put it in the marketplace before further studies were made?

Dr. WEINER. No. My testimony is I think you will find there had been a considerable body of other opinion besides the one you read and my personal opinion is that the other opinion is more correct and that on balance this is an example of wherein the attempt to lean over on a thin line of a possible harmful effect, we have guaranteed the absence of a useful effect for a period time. That is my professional opinion and I recognize that other knowledgeable men may disagree.

Senator NELSON. As I see the language, they say "in those rare instances"—let me read it to be correct—it says, "these two drugs are available for emergency purposes in the occasional patient who may not respond to propanolol, which is available."

Senator KENNEDY. I want to thank the panel.

Mr. Stetler, yesterday there were a number of allegations that involved a number of pharmaceutical companies. I am sure you have a copy of the record. We would invite any comments that the companies may want to make to those charges. We would welcome them and if you want to take on the responsibility of informing them, we will be glad to work with you.

Mr. STETLER. Can I make just a brief comment on that?

Senator KENNEDY. Certainly.

Mr. STETLER. With respect to individual drug products, obviously that would have to be done by the companies. I will look into that.

There was an insinuation, not an outright allegation, that possibly the reorganization within FDA, which really put out of business some particular unit or panel in the medical division of that agency, was caused by an activity of the industry. I honestly think that is not a

fact. As far as I know, to the best of my knowledge, if that is a charge, it is false. Really I think it is not accurate in any respect.

Senator KENNEDY. Dr. Winkler said in his testimony yesterday that the reason primarily was that they wanted to make a management change in the Division and the Division had been a major source of complaints from industry.

Your testimony is that that is not so?

Mr. STETLER. There may have been comments by industry on individual decisions, but to the extent, to put that entity out of business, no, not so.

Senator KENNEDY. Thank you.

[The prepared statement of Mr. Stetler follows:]

Statement of C. Joseph Stetler, President
Pharmaceutical Manufacturers Association

Before the

Subcommittee on Health
Senate Committee on Labor and Public Welfare

August 16, 1974

Mr. Chairman and Members of the Committee:

I am C. Joseph Stetler, President of the Pharmaceutical Manufacturers Association. With me today are Bruce J. Brennan, Vice President and General Counsel of PMA; Lewis H. Sarett, Ph.D., President, Merck Sharp & Dohme Research Laboratories; and Murray Weiner, M.D., Vice President, Merrell-National Laboratories.

We are here in response to your request for the industry's views concerning the status of drug innovation and approval in this country and possible ways of improving the present system.

The subject is not new. Other Congressional hearings and various symposia have explored it. Dozens of papers have been published, and innumerable speeches have dealt with it. Yet this attention has not, in our opinion, solved the dilemma. Opponents in the debate have tended to argue from institutionally biased positions. Some persons in industry and elsewhere have pointed to bureaucratic inefficiency, while some in the FDA have claimed that the research supporting many of the drugs available overseas is below the state of the art in the United States, or that many of them lack significance.

The present hearings provide an excellent opportunity to put the matter into a more balanced perspective from which sound public policy can be determined. Perhaps we need a strong restatement of national interest in the social values of progress in drug therapy. For what is at stake here is the way a unique national asset -- pharmaceutical industry research --

can function most effectively on behalf of medicine and society. On the capabilities of of some 22,000 industry scientists and technicians rests a major share of our responsibility for combating and overcoming the diseases of mankind. Nowhere else does there exist such a degree of insight into the life sciences and their application to the incredibly complex problems of human disease.

It is our hope, then, in the first place, that we can help shift the emphasis from the numbers game, or the politics of blame, to a search for new encouragement and improvement in American drug innovation. We seek to assist in the development of a new level of creative and participatory regulation designed not simply to prevent the marketing of mistakes -- which surely nobody wants -- but to assure that the public reaps the rewards of good science by according it the efficient review it deserves. We look forward to an era of openness where cooperative development and refinement of the regulatory process can prosper to the public benefit.

Fortunately, despite differences between industry and the FDA, some of which we will allude to today, the fundamental trends in the drug review process are upward. What these trends now need is Congressional endorsement. For too long, interest has tended to concentrate unduly on one aspect of FDA activity -- proscription of unsafe or ineffective drugs. It is time, we believe, to examine the other side of the regulatory coin -- FDA's role in influencing the prompt availability of needed medications.

It almost goes without saying that the task of facilitating research productivity is worth pursuing. One has only to examine the most elementary evidence, such as the fact that today's children are likely to live half again as long as their great grandpartents; that the death rate from hypertension is half that of 20 years ago; and that the death rate from infections is now one-fiftieth of what it was in 1900.

In part, these and other dramatic successes, to which pharmaceutical industry research has made important contributions, have permitted great numbers of people to survive longer and therefore be exposed to other diseases as yet unconquered. Thus the cardiovascular disease death rate is half again as large as it was at the turn of the century, and the reported incidence of cancer is triple that recorded 70 years ago. While we have no prospects of making man immortal, medicinal scientists today share with their predecessors a sense of urgency in attacking these remaining disease problems.

From time to time, it has been proposed that only drugs shown to be clearly superior to existing therapy be patentable or marketable. This supposedly would spur the sponsorship of so-called "meaningful" research. Sometimes FDA, following the same approach, has refused to move promptly on what it regarded as minor variations of established medications.

In this light, it is important to remember that the "drug of choice" for most patients may not be the best selection for a particular patient. A "minor" modification may well result in safer and more effective therapy in such circumstances. Slight modifications of known compounds have sometimes led to major unanticipated therapeutic gains. Although the list of such cases is long, perhaps the most prolific field for molecular modification concerns the sulfonamides, which have yielded not only major anti-infectives but advances against diabetes, hypertension, gout and leprosy. Drugs to combat depression have their roots in research against allergy and pain, and the phenothiazine tranquilizers were discovered in the search for better antihistamines. The point is that the modern chemist has learned that subtle changes in chemical structures can produce profound and sometimes unpredicted useful activity. Each time we cancel out a research program thinking it won't yield a breakthrough, we could be missing a benefit that only time would reveal. Therefore, we must take care that the regulatory environment encourages plural approaches and a measure of flexibility out of respect for the therapeutic bonuses which have resulted in the past and which could well emerge in the future.

Charges that the pharmaceutical industry is unduly occupied with research on "me-too" products ignores not only science but economic facts as well. With costs of 10-20 million dollars per product -- without counting additional capital costs -- it is obviously becoming less and less desirable to seek a product which does not represent a significant improvement over available medication. Thus the pursuit of truly important new products is the only sensible course for industry, even though not every research program designed to find a major new therapeutic agent succeeds.

The Time Factor in Drug Development and Marketing

We have referred previously to our sense of urgency in seeking new and improved products. While we fully recognize the importance of maximum safety in the conduct of research, we cannot dismiss the risk of allowing untold thousands to continue to suffer and perhaps die while a potential treatment is being moved forward at less than full deliberate speed. Just a one-year delay in the availability of polio vaccines or anti-hypertensives would probably have accounted for more deaths than all the inadvertent effects resulting from investigational drugs in the United States in the past century. We would, therefore, like to review some of the factors which influence the new drug approval process.

(1) The Efficiency of Research

The British have conducted some interesting investigations through their industry-funded Centre for the Study of Industrial Innovation, as to the relative efficacy of international drug research programs. Their inquiry shows that the American contribution to drug innovation is very large, in fact more than four times as great as Britain's. But they go on to observe that the American pharmaceutical industry spends ten times as much on R&D as does England. These differences in productivity probably lie not so much in the skills of their scientists or research administrators as in the framework within which they have been operating in recent years.

(2) The Investigative Process

All drug research is ultimately influenced by, or conducted under, the IND process. While this process is primarily concerned with reducing the risks of clinical testing to a minimum, it has at times failed to take into consideration the need to balance the risk of clinical testing against the risk of not performing clinical tests. Requirements which prevent or delay clinical testing can, by their very nature, create a degree of risk to the public welfare which must be balanced against the contribution of these requirements to the safety of the testing program.

(3) The NDA Process

While the average processing time necessary for approval of a New Drug Application (NDA) in the last decade has grown progressively longer, it now appears that the time may have peaked. It has not been exceptional recently for the FDA to review and approve an NDA in a year or even less. This is important progress which, unfortunately, is not yet visible in some therapeutic classes, particularly for drugs used in chronic diseases.

An area where improvement has been made is in the acceptance of foreign studies. Until recently, FDA has been unwilling to accept foreign investigational data, so that it has often been necessary to repeat studies already performed abroad. The problem is not yet solved, but at least a regulation is pending to provide for acceptance of suitable foreign studies. The FDA has also begun a program designed to spot relatively important new drugs early in their development and to monitor their progress carefully so as to help assure more prompt approval when warranted by the evidence. And the agency has seen the wisdom of permitting some products to be marketed at the earliest possible time in

view of their particular promise, with special post-marketing studies as safeguards. Hopefully, these changes suggest that in the future fewer drug innovations are going to be kept from American patients longer than necessary.

Drug Availability in Britain and the United States

It is helpful in looking at our situation in the United States vis-a-vis that of Britain to focus on the characteristics most likely to result in the earlier availability of drugs which are safe and effective. Since there is little evidence of countervailing risks facing British patients as a result of these important new drugs reaching them earlier, we hope that both the FDA and the scientific community will search for ways to learn from the British experience. We commend the FDA for its new focus on the circumstances which have delayed the American marketing of useful drugs -- circumstances which are not always the fault of the industry, of the FDA, or of the clinical investigator.

We in industry are prepared to join forces with government in an effort to measure the net social, economic and therapeutic gains (or losses) associated with the availability or absence of reliable new compounds.

In the past three or four years, numerous articles (Selected Bibliograpy attached) have been written about the so-called "drug lag" in the United States, compared with other developed countries. A review of them is basic to any serious study of this subject.

In particular, Dr. William Wardell's incisive articles, comparing the American and the British scenes, are provocative and somewhat disquieting. He has shown that in the ten years ending in 1971, the British physician had a therapeutic advantage over his American counterpart in the use of new drugs most of the time.

Moreover, Wardell found that many of the new drugs available in Britain were regarded as therapeutically important contributions. His most recent paper, delivered at a symposium only last month, suggests that the situation here is improving and that the therapeutic contrast between the two countries is becoming less marked, but that nevertheless, a significant disparity remains.

Other examples from the literature suggest that concern about this matter is widely shared. Writing in the Winter, 1974 "Perspectives in Biology and Medicine", Dr. Leo Hollister commented that a symposium on "New Drugs for Heart Disease" might more accurately have been titled "Drugs American Cardiologists Would Like to be Able to Use". Among the drugs he cited, some of which later became available here, were the beta-stimulator salbutamol; the antihypertensives diazoxide and bethanidine; bretylium for cardiac arrhythmia; and various beta blockers.

Sir Derric Dunlop, from his perspective as the British equivalent to the U.S. Commissioner of the FDA, has contended that "Excessive delay in clearing a valuable new medicine may have results as unfortunate as those arising from the clearance of one which is undesirably toxic".

The Economics of Pharmaceutical Research and Development

One of the apparent effects of the existing situation has been a decline over the years in the rate of growth of research and development investment by the pharmaceutical industry. About 20 years ago the industry was devoting perhaps $50 million annually to R&D. That figure more than quadrupled by 1961. The growth continued over the next decade, tripling by 1970. By 1973, the annual spending had surpassed $800 million, but the rate of growth had slackened. Nevertheless, it appears that the industry will have doubled its dollar commitment to research by the end of this decade, in comparison to 1970. The number of new

compounds that can be subjected to investigation, however, as indicated by investigational new drug exemptions filed with the FDA, is not growing. Furthermore, the number of firms sponsoring research is declining, and the number of firms introducing new drugs each year now stands at less than half of what it was in 1962.

The sponsorship of research is extremely expensive. A great many compounds must enter the research process if any useful drugs are to emerge from it. If one considers that effort as a national resource, created by our scientists, it is worthwhile to ask whether any intrinsically worthwhile drugs are failing to emerge. And if we wish to avoid the concentration of research in fewer hands, it is important to explore ways of encouraging a reversal of the apparent trend away from pharmaceutical research in industry, especially by the smaller firms.

Suggestions for Improvement

As stated earlier, a rather extensive collaborative effort in recent years involving FDA, industry and others has resulted in some progress and a promise of more. We believe the following suggestions, some of which have been discussed extensively with FDA, deserve new or increased attention by the agency.

(1) Sequential IND - Originally proposed by the industry in 1969, this approach suggests the sequential approval at the end of each phase of the IND process.

At a College of Cardiology Conference in May of this year, Dr. Richard Crout, Director of the FDA Bureau of Drugs, renamed the concept a "Developing New Drug Application". A new proposal which will hopefully revive the plan is now in preparation.

(2) Certified NDA Summary - This concept envisions a more expeditious review and the submission of more manageable evidence in support of a New Drug Application with additional responsibility being assumed by the sponsor. The certified summary would contain all pertinent material, with the raw data available for spot-checking and post-marketing audit. Appropriate

penalties would attach to falsification or the withholding of information so as to assure the integrity of the certified summary. This proposal, suggested by industry in 1965, should be actively pursued.

(3) Post-Marketing Monitoring - When a problem arises with a marketed drug there is an understandable tendency to re-examine the pre-market regulatory process which allowed that drug to reach the market. Unfortunately, this tendency can push the demands at the pre-marketing stage to unrealistic limits to the detriment of the public. Rather than pursue the unattainable goal of absolute safety, it appears more worthwhile to improve surveillance systems in the post-marketing period to pick up possible hidden or unsuspected effects.

Since scientific data is never really final, NDA approval should take place at a point where the public good suffers more from delay than from approval of the New Drug Application. Planned monitoring, after marketing, should be recognized as a legitimate approach in the best interest of patients.

(4) Use of "Outside" Advisors - Outside consultants and expert advisory committees can speed and strengthen the drug review process. Major progress has been made by the FDA in this area in the last several years. The question of conflict of interest, which is frequently raised must be balanced against the "conflict of disinterest" which can result from the selection of advisors who lack meaningful experience.

(5) International Drug Monitoring - Various studies have shown not only that there are long gaps in time between the introduction of drugs in other developed countries and in the U.S., but also that there is little awareness about even widely used drugs from place to place. It would therefore seem worthwhile to use an available international network to assemble information on new drug developments and to circulate it in a systematic way. Thus periodic checks could be made on the status of new drug introductions world-wide.

In addition, there are legislative approaches, some relating to the "drug lag" and some of a more general nature which we believe are needed as well. Among them:

(1) A Review of the 1962 Drug Amendments - In general, the 1962 Amendments to the Food, Drug, and Cosmetic Act are sound and they had and have our support. But in their wake a mood has developed which tends to encourage resistance to innovation, a mood that may even endanger scientific progress. Thus an expression of public policy in favor of innovation in health care would be most desirable. In our view, the time is fitting for a thorough and objective public review of the legal and regulatory climate under which drug research is conducted. This review should seek to highlight the objectives which the public, the professions, the FDA, and the industry share, and to lend the weight of national prestige to some changes in attitude or law that would help meet those ends and benefit the entire Health Care System.

(2) Refinement of FDA Demands for Records and Reports - The statutory authority given to FDA requiring records and reports on clinical experience with new medicines is basically sound. However, that authority has been interpreted so broadly that every manufacturer now submits practically every report and every published article about every product which he manufactures. The resultant duplication of reports by multiple manufacturers on identical drugs, and the glut of paper shipped to FDA, buries needed information in stacks of unread material, thus subverting the intent of the law. In our view, only records and reports of clearly significant experience should be sent to the agency. Existing legal provisions are more than adequate to deal with any improper withholding of such information. Preferably, too, an industry-wide system could be developed for the submission of published data on marketed drugs through the facilities of the National Library of Medicine or other bibliographic services.

(3) A Redefinition of the Term "Substantial Evidence" - Prescription drugs marketed between 1938 and 1962 are subject to review and to the requirement that "substantial evidence" of effectiveness be submitted. In addition, a new drug permitted on the market in the United States, is subject to later removal if new evidence regarding its effectiveness causes concern. Much experience and knowledge accumulates with every drug in general use. Yet under today's law this body of knowledge is given little, if any, weight in deciding whether to permit the drug to remain on the market. Under the law and current FDA regulations, if a drug becomes suspect in FDA's opinion, the same type of extensive testing required to first market the product would have to be repeated in order to re-prove its effectiveness.

We urge an amendment which would recognize the opinions of qualified experts as acceptable evidence in support of a product's effectiveness. This would place the emphasis on the judgment of the experts and not simply on a specified type of evidence. The amendment would not affect the initial review of a new drug in the original NDA process, but would only apply to marketed products whose status, with respect to effectiveness, comes into question.

(4) Provision for Appeal of FDA Actions Stopping Drug Investigation - At present, an FDA decision to cancel an investigational new drug exemption, which in effect ends the investigation of that drug by the manufacturer, is not subject to any appeal. One court has concluded that to question an adverse action by the FDA, a sponsor must file a full NDA and then apply for a hearing when the NDA is rejected. That exercise wastes both sponsor and FDA resources, and it could be avoided with the enactment of a rational legislative remedy providing for appeal.

(5) Independent Review in the Case of Requests for Administrative Hearings - Present practice at FDA is to brand an administrative hearing on a dispute involving a new drug only when such a hearing is considered appropriate by the agency. In effect, this procedure gives

one party to the dispute total control over its disposition. Fairness and order suggest another procedure. We recommend an amendment to the law that would permit an independent expert panel to review the scientific issues in such cases, with appointment of the review panels by an appropriate prestigious scientific organization. Such a mechanism would resolve disputes effectively at the informal inquiry level and make formal hearings unnecessary in most cases. This method for resolving scientific issues is already a part of the law with respect to pesticide, chemical and color additive petitions and, where employed, it has been quite effective.

Each of the recommended proposals, standing alone, may not loom as of paramount significance. But taken together, they comprise a program that could, in our opinion, effectivaly advance drug therapy as an even more integral, high technology factor in the nation's evolving health care system.

Mr. Chairman, this concludes our formal presentation. We will be glad to answer questions.

Attachment

The Status of Drug Innovation in the United States

A Selected Bibliography

Carlova, John. "Are Useful New Drugs Being Bottled Up by Bureaucracy?" Medical Economics. August 6, 1973. p. 94.

Chain, Ernst B., FRS. "Academic and Industrial Contributions to Drug Research." Journal of the Royal Society of Arts. Vol. CXI. October, 1963. p. 856.

De Haen, Paul. "New Drugs in Europe." New York State Journal of Medicine. March 15, 1973.

De Haen, Paul. "Pitfalls in the Analysis of New Drug Introductions." Product Management. November, 1973. p. 48.

"Drug Lag; Why the U.S. Suffers from It." American Druggist. March 6, 1972. p. 29.

Fudenberg, H.H. "The Dollar Benefits of Biomedical Research: A Cost Analysis." The Journal of Laboratory and Clinical Medicine. Volume 79, No. 3. March, 1973. p. 353.

Hollister, Leo E. "The FDA Ten Years After the Kefauver-Harris Amendments." Perspectives in Biology and Medicine. Winter, 1974. p. 242.

Lasagna, Louis, MD, and Wardell, William, BM, BCh, DPhil. "An Analysis of Drug Development Involving New Chemical Entities Sponsored by U.S.-Owned Companies, 1962-1974." Paper delivered at the Conference on Drug Development and Marketing, American Enterprise Institute for Public Policy Research, July 25-26, 1974.

Lewis, Thomas, MD. "The Future Impact of Science and Technology on Medicine." Presented at the Squibb Institute for Medical Research, Princeton, N.J. October 11, ~~1974~~ 1973.

Ley, Herbert L., Jr., MD, MPH. "Problems in the Development of New Drug Entities: U.S. Role in International Research and Development." Presented at the annual meeting of the Research and Development Section, Pharmaceutical Manufacturers Association, Naples, Fla. May 7, 1974.

Modell, Walter, MD. "Where Are the New Drugs?" Cardiovascular Review. 1971. p. 103.

Reis-Arndt, E. and Elvers, D. "Results of Pharma Research; New Pharmaceutical Agents 1961-1970." Die Pharmazeutische Industrie. 1972. 34:181.

Ross, Walter S. "The Medicines We Need - But Can't Have." The Reader's Digest. October, 1973. p. 97.

Sadusk, Joseph F., MD. "The Effect of Drug Regulation on the Development of New Drugs." Paper presented at Symposium on Clinical Pharmacological Methods - Phase I & II, New Tulane University, New Orleans, La. March 23, 1973.

Sarett, Dr. Lewis H. "The Impact of the F&DA on Industrial Research and Development." Paper presented to the Industrial Research Institute, panel on "Impact of Regulation on Industrial R&D," Chicago. October 18, 1973.

Teeling-Smith, G., et al. "Innovative Activity in the Pharmaceutical Industry." Papers presented at a conference organized by the National Economic Development Office, May 3, 1973. Chemistry & Industry. June 2, 1973. p. 502.

Tishler, Max, PhD. "Drug Discovery - Background and Foreground." Clinical Pharmacology and Therapeutics. July-August, 1973. p. 479.

Wardell, William M., BM, BCh, DPhil. "Introduction of New Therapeutic Drugs in the United States and Great Britain: An International Comparison." Clinical Pharmacology and Therapeutics. September-October, 1973. p. 773.

Wardell, William M., BM, BCh, DPhil. "British Usage and American Awareness of Some New Therapeutic Drugs." Clinical Pharmacology and Therapeutics. Vol. 14, No. 6. November-December, 1973. p. 1022.

Wardell, William M., BM, BCh, DPhil. "Therapeutic Implications of the Drug Lag." Clinical Pharmacology and Therapeutics. Vol. 15, No. 1. January-February, 1974. p. 73.

Senator KENNEDY. Our next witness is Dr. Schmidt, who is the Commissioner of the Food and Drug Administration.

Dr. Schmidt, we want to swear you in as we swore in the other witnesses.

Do you swear to tell the truth, the whole truth and nothing but the truth, so help you God?

[Alexander Schmidt and J. Richard Crout answered affirmatively.]

Senator KENNEDY. Dr. Schmidt, as I am sure you are aware, we heard some extraordinary testimony yesterday by a number of the employees that were subpenaed by this committee. They did not seek us out. We sought them out. Their statements and comments, as I am sure you are aware, indicated harassment in the Food and Drug Administration when they made decisions that were contrary to the pharmaceutical industry's interest. They talked about pilfering of their files, directions to change memorandum, and being excluded from meetings. They said that advisory committees in many instances upheld their scientific findings. We heard from members of advisory committees who felt they as well were harassed and inopportuned, to put it gently. Then the point was made by all that they had been transferred out of their primary areas of training and competency to work in other areas.

These are exceedingly, serious allegations, and that is why we are glad to have you up here this morning to make what comments you will on any of the testimony that we heard yesterday and any other issues on which you want to comment.

STATEMENT OF ALEXANDER McKAY SCHMIDT, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, HEW; ACCOMPANIED BY J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS, FDA; AND WILLIAM W. VODRA, OFFICE OF GENERAL COUNSEL, FOOD AND DRUG DIVISION, HEW

Dr. SCHMIDT. Thank you, Mr. Chairman.

Before I begin, I would like to introduce my colleagues. On my right is Dr. J. Richard Crout, Director, Bureau of Drugs; and on my left is Mr. William W. Vodra, a member of the Office of General Counsel.

I am pleased to appear before the subcommittee this morning for essentially the same reasons you just mentioned. Yesterday you said that you considered these hearings of prime importance; I agree. You said that the American people depend on the FDA to assure the safety and effectiveness of their drugs; I state that the FDA can warrant that trust. You said that the purpose of these hearings was to sort out the facts; I believe we can contribute to that important goal.

Mr. Chairman, with your permission, my remarks this morning will be completely different from the formal testimony submitted to you; the reason needs to be explained.

I would add that I tried to have what I am about to say typed up this morning hurriedly and that there are typographical errors in it, and for this I apologize.

Senator KENNEDY. You will be able to make whatever changes are needed for the record.

We will include your other statement in the record if you so desire.

Dr. SCHMIDT. I would wish that the formal statement be put in.

Senator KENNEDY. It will be done at the conclusion of your testimony.

Dr. SCHMIDT. While we received no written invitation to this hearing, we were told by your staff that the subject was to be connoted by the words, drug lag. We have therefore prepared a carefully documented and, I think, excellent statement of our position in regard to the so-called drug lag.

I learned early this week of your intention to subpena FDA employees as witnesses, and heard yesterday afternoon something of the testimony you received from them. Last night and this morning I read the wire service stories and articles in newspapers. I then decided I must speak on the issues at hand, rather than those in my testimony.

Senator KENNEDY. I must say that the testimony heard yesterday relates to the availability of drugs to the public and so therefore, it is related to the question of drug lag, but continue.

Dr. SCHMIDT. My prepared testimony deals with the number of new drugs approved in this country, as compared to the number approved elsewhere. It discusses the reasons for the existing differences in these numbers.

It gives our answer to the questions of whether or not there is a drug lag, and whether or not any lag is serious and needs attention. My testimony thus concentrates on the results of our decisions, not how we go about making our decisions, so I would agree that the two subjects are certainly intimately related, and what I will say this morning relates more directly to the subjects touched on yesterday.

I hope that at a later time we can return to the subject of my prepared testimony because I think it is important and relates to some of what was said earlier today.

It occurred to me as I read the wire and newspaper stories that it would be tragic indeed if public confidence in the FDA or the morale of thousands of dedicated FDA employees were in any way undermined by the testimony you received yesterday from 11 individuals selected by your staff after they had searched through our files.

I am reassured by the knowledge that you, the press, and the American people all know that the FDA is, and perhaps should be, constantly in the middle of controversy. Everyone also knows that one does not fairly draw any conclusions from hearing only one side of a controversy.

Mr. Chairman, as you pointed out yesterday, one side of this controversy charges that FDA officials approve drugs that are too toxic for the American market, and then apparently rage against anyone who tries to hold the drug back.

The other side of the controversy charges the same FDA officials with keeping off the market drugs that would be valuable additions to the therapeutic armamentarium of the American physician.

The first point everyone should appreciate is that the drugs both sides are talking about are one and the same; which points up the dilemma nicely.

Senator KENNEDY. I do not understand your dilemma, Mr. Commissioner, quite frankly. One side has a special interest in getting the drugs out on the market, and that is the pharmaceutical companies, and as interested as they are in the health of the American people,

they are also in it to make a profit on it. Is that one side of the dilemma?

Dr. SCHMIDT. No.

Senator KENNEDY. And combined with that are physicians who want to be able to prescribe as they want to without any kind of interference.

Now the other side is that your agency is supposed to protect the public interest. That is not the other side of the dilemma because your first interest ought to be as charged by the Congress and the statute—the safety and the efficiency of drugs, as they relate to the consumer's interests. So how do you say on the one hand we have black and on the other hand white, and therefore we have to do something in between?

Dr. SCHMIDT. Well, I can answer that in two ways. Perhaps it would help if I had before me your statement of yesterday—well I thought I was paraphrasing you in pointing up the dilemma. In your statement yesterday you said that on the one side there are those who feel that the FDA is holding back valuable drugs and on the other side are those who say that the FDA is permitting dangerous drugs to be on the market.

The only point I am making is that you accurately described a dilemma and, that is, that two different viewpoints are talking about the same drug. That is the sole point I am making.

Senator KENNEDY. The fact that dedicated scientists felt pressure from the drug companies all the way along the line, that as a result of direct pressures from drug companies they were harassed, they had their memoranda and scientific testimony altered, that is the thrust of the testimony. Now that is an entirely different issue from attempting to assure the safety and efficacy of drugs for the public interest. That is what your department is supposed to do. The testimony of yesterday indicated that the power and the influence of the drug companies was the most powerful influence that these dedicated, eminent scientists were facing.

That is the dilemma. That is the point I would hope you would address this morning.

Dr. SCHMIDT. I think we can and will talk to that issue.

Senator KENNEDY. Fine.

Dr. SCHMIDT. The second point to be emphasized is that, by and large, both sides appear to me to be acting in good faith from an honestly held opinion, and that includes the individuals who were before you yesterday. It is also noteworthy that the majority of those who think there is a drug lag are the physicians of this country; they are opposed often by rigorous toxicologists.

It is quite ironic, Mr. Chairman, that one week the House of Delegates of the American Medical Association can vote to seek repeal of the 1962 amendments to the drug laws, because the FDA impedes the release of new drugs; a week or so later the Journal of the American Medical Association carries an editorial by a well-known cardiologist who castigates the FDA for keeping valuable antihypertensive agents, including propranolol, off the American market. A week or so later, we are accused here in your hearing of flooding the market with dangerous drugs, including propranolol.

If one side says black, and another says white, and I have to choose one or the other, then I am obviously in trouble, especially if the truth

is really a shade of gray. That is not to be interpreted as an oversimplification.

Senator KENNEDY. You say you were accused of flooding the market with dangerous drugs. I sat through the whole hearing yesterday and did not hear that allegation made. There were many others, but not that. It seems to me that FDA is not balancing industry interests with the public interest. It always comes down in favor of industry.

Dr. SCHMIDT. You are clearly assigning white hats and blacks hats, and I am not prepared right now to do that.

Senator KENNEDY. I am not. I am assigning the white hats to the FDA. I think they ought to be the ones that make the decisions and not be adversely influenced by the drug companies. That is what I am saying.

Dr. SCHMIDT. I certainly agree with that.

Senator KENNEDY. But what we heard yesterday was that the power of the drug companies had great impact on the decisions that were being made.

Dr. SCHMIDT. I would hope in a few minutes we could spend some time on the process now in existence so that we could discuss how the influence might or might not be laid on our officers.

Senator KENNEDY. All right.

Dr. SCHMIDT. It has been my repeated observation that those who take one side or another of this controversy often take an extreme position, and this is understandable. Some seem to want little or no drug regulation, and others seem to want few or no drugs.

It has also been my observation that people try to do their jobs well. It is natural and proper for a toxicologist to be more concerned about toxic effects, and to emphasize such to the general populace, than to agonize over the balance of a benefit-risk equation. It is obvious that some drugs, risky as they may be to some, may be lifesaving to a small but finite population.

Senator KENNEDY. That was not by and large the drug we were talking about yesterday, but you may proceed.

Dr. SCHMIDT. Well, I had the disadvantage of not having been here yesterday, but I am told that yesterday it was implied, if not stated explicitly, that FDA held to a dual standard with regard to recommendations of reviewing officials, paying more attention to negative views. Mr. Chairman, yesterday you gave evidence of concern and distress over this, and I must reassure you. We have no dual standard.

Every citizen, private or corporate, has a right to petition his Government. If the Government grants the petition, it is obvious that all parties agree, and there is no controversy. But I look upon the denial of a petition as another matter, worthy of our best care and attention, and that includes review of controversy. I do not want any single individual denying Mr. Ralph Nader's petitions to us, or your petitions, or industries'.

I became Commissioner of Food and Drugs 13 months ago. I brought with me some strongly held beliefs, which I am determined to see guide the FDA in its operation. I found that Dr. Crout shared my beliefs, and I appointed him Director of the Bureau of Drugs.

In conversation with Dr. Crout, in appearances before the Bureau of Drugs personnel, in testimony elsewhere, in speeches, and in other settings, I have verbalized and written FDA policy that will, at least

during my tenure as Commissioner, have to be followed. Some of the policies were begun by my predecessors in office, but that is irrelevant to my enforcing them now.

Since the policies relate directly to how the FDA operates, they are relevant to yesterday's discussion. I would like, therefore, to state my beliefs and the resulting policies, explicitly, once again. And I know that what I am about to say really speaks directly to one comment you made this morning, that the charges yesterday depict a closed system of drug review with little or no public accountability or input. That does not pertain, and I hope we can talk about that, to the situation that exists now.

Senator KENNEDY. Let's talk about it right now. Let me give you an example of what we and some of the witnesses were concerned with yesterday.

This is a memorandum dated May 16, 1974. Your reservations and those of Dr. Bryant concerning the lack of raw data are noted. I would appreciate it if Dr. Bryant nevertheless would update his summary as requested by Dr. Belton in his memo of April 26, 1974, as though he were willing to accept the published reports as being totally accurate and reflective of raw data.

This appears to me to be a memorandum indicating FDA knows that someone who is doing staffwork wants the raw data, but gives an instruction that he will accept the published reports as being totally accurate and reflective of the raw data.

Here is a memorandum to the Commissioner from the director executive secretary, dated December 1, 1972, regarding a staff meeting with the Commissioner of the Bureau of Drugs.

I will submit all of these memos for the record. But point No. 3 says: "The Bureau has adopted the policy of destroying verbatim transcripts of advisory committee meetings as soon as the summary minutes have been approved by the committee."

Here is a memorandum in 1973 from Mr. Belton to Dr. Bryant. I will make this a part of the record.

Third paragraph: "Attached to this memo is a copy of the official minutes of the advisory committee. This should be inserted into the IND, and your own copy of the minutes ought to be removed."

These are written memorandums that substantiate and support the eloquent testimony of people who have worked in your agency for a number of years, about what is happening.

I am interested in what comments you want to make.

Dr. SCHMIDT. With your permission, I would like to take a very few minutes and draw some general policy orders that I have laid out that now guide what this agency does. Then I would return to the specific question because I would like to lay this out as a kind of preamble—which we are fond of—laying out to the specifics.

Senator KENNEDY. Whatever way you want to proceed.

Dr. SCHMIDT. Very explicitly, first, to the fullest extent possible, FDA decisions must be based on scientific evidence, not personal prejudice.

Second the scientific evidence we use must be sound and must be accurately analyzed and evaluated.

Third, the arguments used by the agency in decision making must begin with truthful premises and proceed in a logical and valid fashion to sensible conclusions.

Fourth, whatever we do must be subject to peer, and public, evaluation. Mr. Chairman, part of the bedrock of excellence in science is peer review, as you well know. Holding one's work up to the harsh light of public exposure is an integral part of scientific integrity.

The FDA is not playing poker, wherein holding one's cards close to his vest is both proper and wise. The FDA must, to the extent allowed by law, lay all of its cards face up on the table.

I am insisting that we be able to explain, openly, honestly and well, what we do, why we are doing it, and what the bases are, scientific or otherwise, for our doing it.

The FDA is engaged in vitally important public business, and the public must be a part of it. I think so, and several prestigous groups evaluating the FDA in years past have so advised us.

Senator KENNEDY. Let me quote from the following: "I am insisting that we be able to explain openly, honestly, what we do, why we are doing it, and what the bases are, scientific or otherwise,". What does "otherwise" refer to?

Dr. SCHMIDT. The Food and Drug Administration, we have tried to establish, is a scientific regulatory organization whose business it is to protect the public in a variety of ways. Scientific evidence, and the application of it, is a principal basis. Others are regulations, the law education, both public and professional—there are many bases for taking action. Our preambles, for example, are trying to lay out not only the scientific, but also the other bases of our regulatory action and explain what the philosophy is. We devoted considerable time to that Wednesday morning in regard to the vitamin-mineral regulations in which part of the basis was scientific, but part was regulatory and philosophical—that is what I mean. Because of our desire for an open and public review of what we do and how we do it, we have established advisory committees to me, and advisory committees to the Bureau of Drugs. The latter are our professional peers, appointed because of their eminence. They are to advise us, to monitor us, and to help us achieve the wisdom and balance necessary for our proper functioning.

I will insist that our scientific reviews lay out, in precise detail, the safety and efficacy issues involved with a drug, or a food additive, or a medical device—and do it accurately, well, even elegantly.

And then I will insist that our reviewing officers be willing—no, be desirous—of subjecting their work to review by competent and qualified peers, or by an advisory committee, or by me.

This is as it must be. Our work is far too important to depend on the evaluation of any one person. In point of fact, our decisions must depend on the widest and best advice we can find, for the issues usually are not, contrary to what you might hear, clear-cut and universally held. This includes opinions about the toxic potential of drugs. Nor is the truth lodged always with one person. Now these policies I have laid out; I have laid out explicitly to the personnel in the administration.

If anyone is unwilling or unable to abide by these policies, I will find someone else who is. If anyone believes it wrong that advisory committees, or bureau superiors, or other competent peers be asked to review scientific work, I will find others who believe it entirely proper.

Senator KENNEDY. Those are fine sounding words and certainly I am sure represent the ideal, but they are just not being lived up to at the present time.

For example, we had testimony yesterday from Dr. Apter who said: "With respect to propranolol, since we have gone specifically on record as not recommending propranolol for angina, and yesterday I saw a letter signed by Dr. Crout and dated September 4, 1973, and sent to Ayerst, saying that the advisory committee had recommended the drug for angina."

Then I asked: "This is misrepresenting your conclusion?"

Dr. Apter said: "It misrepresented the advisory committee's decision, yes."

Dr. SCHMIDT. If I could say two things. First, I must agree that in times past there may have been instances in which pressure was applied or something happened. The charges that were made are terribly important. I agree with you. I assure you that, given the specific instances, we will investigate these, and I would welcome your committee's oversight of my investigation. At least two of the charges that were aired yesterday have been subject to formal investigatory procedures consistent with Civil Service regulations.

The issues that I can speak to are the procedures being followed now in the instances that may have occurred recently. The second point I would like to make is that events can be interpreted differently by different people and it is clear to me that in some of the instances that were put before you, people chose to interpret what happened in one way, and I believe that other interpretations are equally valid. I would beg of you not to draw conclusions on the basis of one interpretation of an event.

Now to be specific about Dr. Apter, the conclusion you drew is, from the evidence I have, wrong.

What she said to you is wrong in that we had the decisions reviewed and we had the committee's opinion on the drug which, I believe, differed from Dr. Apter's opinion.

Now this was in point of fact the subject of a full congressional hearing. There was an extensive hearing on this. Dr. Crout may be able to clarify very quickly for you that last example you brought up, if you wish.

Dr. CROUT. The Cardiovascular and Renal Advisory Committee voted 4 to 1 to approve propranolol for angina pectoris. The one was Dr. Apter, dissenting.

We will be happy to supply the memoranda, minutes, whatever you might like, to document the committee's recommendations to us, the recommendations that came to me.

[The information referred to follows:]

ADVISORY COMMITTEE RECOMMENDATION CONCERNING

USE OF PROPRANOLOL FOR ANGINA PECTORIS

Attached are documents provided by the Food and Drug Administration to substantiate that the Cardiovascular and Renal Advisory Committee approved the inclusion of angina on the label of propranolol, by a vote of four to one. These documents are:

1. Excerpts of transcript of the April 13, 1973 meeting of the Advisory Committee showing its decision with respect to propranolol for angina.

2. The minutes of the closed session of the April 13, 1973 meeting of the Advisory Committee.

3. Memorandum to the file dated March 18, 1974, for NDA 16-762 concerning Approval of Propranolol for Angina Pectoris, by J. Richard Crout, M.D., Director, Bureau of Drugs.

The issues involved in FDA's approval of propranolol for angina pectoris has already been fully explained in extensive and detailed hearings held earlier in 1974 by the Subcommittee on Intergovernmental Relations of the House Committee on Government Operations. The record of these hearings provides a full public record of this decision, and includes the entire transcript of the advisory committee meeting in question beginning on page 296. We have also provided the staff of the Subcommittee on Health of the Senate Committee on Labor and Public Welfare with a copy of this transcript. At the House hearings, representatives of FDA conceded that the minutes of the closed session of the April 13, 1973 Advisory Committee meeting were inadequate. However, the Food and Drug Administration believes that review of the transcript of the meeting clearly shows that the Advisory Committee voted to approve propranolol under certain conditions for use in angina pectoris.

The Agency's procedural regulations will provide more guidance to the executive secretaries of FDA advisory committees as to the appropriate amount of detail in minutes. Pending promulgation of these procedures, the Commissioner has issued a memorandum establishing interim procedures for the development of minutes by executive secretaries of Agency advisory committees. This memorandum is attached.

Transcript of Proceedings

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

- - -

CARDIOVASCULAR AND RENAL ADVISORY COMMITTEE

- - -

CLOSED SESSION

- - -

Rockville, Maryland

Friday, 13 April 1973

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NATIONWIDE COVERAGE

CLOSED SESSION

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

- - -

CARDIOVASCULAR AND RENAL ADVISORY COMMITTEE

- - -

Conference Room A
Parklawn Building
Rockville, Maryland
Friday, April 13, 1973

The closed session of the meeting was convened at 1:10 p.m., Dr. James Warren, Chairman of the Committee, presiding.

COMMITTEE MEMBERS PRESENT:

Dr. James Warren
Dr. Lawrence Wesson
Dr. Noble Fowler
Dr. Eric Feigl
Dr. Julia Apter

COMMITTEE MEMBERS NOT PRESENT:

Dr. Edward Frohlich
Dr. Wilbert Aronow

OTHERS PRESENT:

Dr. John B. MacGregor
Dr. Edward Belton

* * * * * * *

DR. WARREN: * * *

Let me try my thing here. Let's just take two or three sort of straw votes. They're really votes though.

Is there anybody here that wants to recommend to the FDA that an unqualified addition to the indications for the use of this drug be added to -- be approved and added to the package insert, that it is to be used in angina -- sort of "period"? Does anybody want to do that?

DR. WESSON: How would you phrase that?

DR. FEIGL: Wait. He's going to give us the options. How many options have you in mind?

DR. WARREN: I thought everybody would just say "no," that they don't want to do that.

DR. WESSON: You say "unqualified"?

DR. WARREN: Unqualified.

The two options then are that we want to make a qualified statement pointing out the frailties of the evidence and pointing out some of the restrictions on its use -- that would be option No. 2 -- and option No. 3 would be to in effect stick with the earlier decision, thereby recommend no change in the package insert.

DR. WESSON: I think that it should be allowable for the symptomatic relief of angina without recommending it. By recommending it would be to come to the point of view that that should be the first drug of choice, which some people would recommend.

DR. WARREN: This would be how you'd write it up?

DR. FEIGL: Too much semantics.

DR. WARREN: This is how you'd write it up? Okay. You have got three choices. Is anybody in favor of the sort of unqualified listing of this as an indication?

(No response.)

Let me go to the other end. How many here feel that with the evidence at hand, these papers and everything, that we should stick by the earlier decision to say there is inadequate evidence to make a judgment and therefore angina should be left out of the list of indications?

DR. APTER: Pending further evidence.

DR. WESSON: I think there is an enormous but not yet measured element, a glorified placebo and the use of propranolol for angina.

DR. APTER: In fact, you said a lot of people feel better with propranolol. A lot of people feel better with the placebo.

DR. WESSON: Now, part of the benefit from a placebo is the enthusiasm with which the physician

prescribes it, emphasizes it, "This is a potent drug," and the patient that has all this nice feeling all over, he knows he's getting a potent drug. And the physician knows when he's giving propranolol and when he's giving the mannitol tablets.

And I think that when you have extreme enthusiasm on the part of the physician giving a drug and he can point to that scientific rationale for it, you're going to have an immense benefit.

DR. WARREN: I'm just trying to get you to bite the bullet and say you either want to have no change in the package insert or --

DR. WESSON: I'm a great believer in the laying on of hands when the patient feels better. Let's put it that way.

DR. FEIGL: He wants you to raise your hand at one of three.

DR. WARREN: All right. Let's take a vote. There is not support for an unqualified statement, is there?

DR. FEIGL: Okay, just call for the vote.

DR. WARREN: Let's vote for two things:

(a) That we recommend the FDA not change the package insert until more evidence is in.

Or the alternate is going to be some sort of qualified statement about the use of the drug in angina be

prepared.

Okay. How many favor no changes in the package insert?

(Dr. Apter raised her hand.)

DR. WARREN: One vote. Dr. Apter.

How many favor an addition to the package insert mentioning angina in a qualified way?

(Hands raised by Dr. Feigl, Dr. Fowler, Dr. Wesson and Dr. Warren.)

DR. WARREN: Well, that carries. I think, if I may say, the split vote shows the two views about it.

DR. APTER: Not really split, but may I say that here is a situation where you as a scientist said we should not have this in the package until we had more evidence, and you got no more evidence but you got pressure from physicians who had been using it illegally, and that has influenced you. Am I saying it correctly?

* * * * * * *

DR. WARREN: So let me summarize just so we understand it, and then you decide if this is how we want to leave it.

First of all, we have taken a vote, and it came out I think 4 to 1 in favor of recommending the introduction of a statement under the indications segment on the package insert in a qualified way mentioning the use of the drug in angina pectoris.

I carefully avoided saying "recommending the use."

The qualifications would relate that we in general didn't think it was particularly useful in mild,

infrequent angina, and that there should be a particular caution in people who have had heart failure and maybe some other things that we will think of when we write up these statements.

That's the second, the real action of the committee.

* * * * * * *

FOOD AND DRUG ADMINISTRATION

BUREAU OF DRUGS

MINUTES

Tenth Meeting (Closed Session)

FDA Cardiovascular and Renal Advisory Committee

Conference Room A
Parklawn Building
Rockville, Maryland
Friday, April 13, 1973

The meeting (closed session) was convened at 1:10 PM. Dr. James V. Warren, Chairman, presiding.

Committee Members Present:

Dr. James Warren
Dr. Lawrence Wesson
Dr. Noble Fowler
Dr. Eric Feigl
Dr. Julia Apter

Committee Members Absent:

Dr. Edward Frohlich
Dr. Wilbert Aronow

FDA Staff Present:

Dr. Edward Belton
Dr. John MacGregor - Executive Secretary

The committee considered the data available to it from studies, from the literature, and from the material presented in the open session. The committee concluded that these data establish that propranolol is

safe and effective under certain conditions of use for the treatment of angina pectoris.

The committee felt that more information was needed to further establish the definitive role of propranolol in the treatment of angina pectoris. However, the extent to which the drug is now used by physicians in angina leads the committee to accept its use under well-defined labeling conditions. The committee will prepare written reports reflecting these labeling conditions which will aid the division in writing the labeling.

No date was set for the next meeting - such to be determined later.

These minutes have been reviewed and approved by the committee chairman.

J. B. MacGregor, M.D.
Executive Secretary

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : The File for NDA 16-762

DATE: March 18, 1974

FROM : Director
Bureau of Drugs, HFD-1

SUBJECT: Approval of Propranolol for Angina Pectoris

At hearings before the Subcommittee on Intergovernmental Relations, Mr. L. H. Fountain, Chairman, held on March 7, 12 and 13, Mr. Fountain and his staff challenged the FDA to identify the adequate and well-controlled trials supporting the safety and effectiveness of propranolol for angina pectoris. According to their reading of the record, the Cardio-Vascular and Renal Advisory Committee reviewed a package of 33 published clinical studies submitted by the firm and was unable to locate any which they considered to be adequate and well-controlled. Nevertheless, the committee recommended at its meeting of April 13, 1973, that the drug be labeled for use in selected patients with angina pectoris.

Subsequently, Dr. E. D. Belton, Director of the Division of Cardio-Renal Drug Products, recommended approval of propranolol for selected patients with angina pectoris. His "Summary of Basis of Approval" included the following statements: "The labeling as outlined in this review reflects the literature review and recommendations made by the Cardio Pulmonary Advisory Committee in their meeting of April 13, 1973. It also reflects the conclusions drawn from the literature by the Division from the review of the studies from the literature submitted in support of this indication. Although every study submitted did not in each instance meet all criteria, as a group they do provide evidence of a well-controlled quality to support safety, and efficacy." The medical officer's review of the studies submitted did not precisely identify by name any adequate and well-controlled clinical trials. From this record the staff of the subcommittee drew the conclusion that the FDA had approved propranolol for use in angina pectoris in the absence of two adequate and well-controlled clinical trials meeting the criteria outlined in 21 CFR 130.12.

I disagreed with this characterization of the decision and was asked to provide a memorandum for the record outlining my thinking as the responsible public official with sign off authority for New Drug Applications.

I am happy to provide such a memorandum. In my opinion, the package submitted by the firm contains 13 adequate and well-controlled clinical trials which meet the requirements of 130.12. In addition, there are nine other studies which have only minor deviations from the regulations. The specific references to these trials are listed in Appendix A. Twenty of these 22 adequate and well-controlled trials provide evidence of effectiveness, while two do not. Of the two which do not, an appropriate explanation for lack of effectiveness is apparent in one, the study by Srivastava. In this study, the first controlled trial ever conducted with propranolol in patients with angina, the dose of propranolol used was too low, 30 to 60 mg. per day. Subsequent studies have shown that doses of 120 to 360 mg. per day are necessary. In the other study which failed to show evidence of effectiveness (Aronow), the reason for this finding is not clear, and the author did not conclude that the drug lacks effectiveness.

In citing these studies, I would make it clear that they all relate to the short term use of propranolol in the treatment of patients with moderate to severe angina pectoris. Most of these studies were conducted under double blind conditions and were crossover in design. Some were single blind, the period of treatment with propranolol was usually 2 to 4 weeks. Measurements of effectiveness included exercise tolerance tests in some studies, subjective evaluations (tablet counts of nitroglycerin, global ratings, etc.) in other studies, and all of these types of measurements in a few studies. I would also emphasize that not every one of these studies was perfect in its execution. A number of investigators noted that patients developed slow heart rates when on propranolol. Thus the attempts at blinding were not always totally successful. Also, in some studies there were technical deviations from the regulations, such as failure to describe precisely how the diagnosis of angina pectoris was made or failure to state precisely the statistical test used in evaluating the data. These deviations from ideality are common in all clinical trials and may be considered "state of the art" problems. But they are insufficient to detract from the fact that these trials were all well designed, reasonably well executed, and adequate to demonstrate the point--namely that propranolol is effective in relieving the pain of angina in short term trials lasting 2 to 4 weeks.

When the recommendation for approval of propranolol in angina pectoris was sent to my office, I reviewed the transcript of the Advisory Committee meeting of April 13, 1973, the medical officer's review, Dr. Belton's Summary of the Basis of Approval, and the studies submitted by the firm. I noticed that neither the Advisory Committee nor the reviewing personnel had identified specific well-controlled clinical trials but had instead chosen to state that the

trials in totality provided substantial evidence of safety and effectiveness. In reading over the trials it became apparent that they all related to the issue of the short term use of propranolol in angina while the proposed new indication related to the long term use of propranolol in angina pectoris. Thus the proposed labeling for use in angina pectoris was in fact based on an extrapolation from the data in these short term trials and from the experience of qualified experts who spoke before the Advisory Committee at its meeting on April 13, 1973. While I did not review every study in detail on that occasion, I reviewed a sufficient number to assure myself that at least several adequate and well-controlled clinical trials were present in the literature and had been submitted by the firm. Before signing off on the application I did not record my thoughts in a memorandum because I was basically concurring with the recommendation of the Division, albeit for reasons in addition to those offered in Dr. Belton's Summary of the Basis of Approval.

It literally never occurred to me that an outside party reviewing the files of this drug application might infer from the remarks of an Advisory Committee considering labeling for long-term use that the drug was literally not effective at all in patients with angina pectoris. In retrospect, I can appreciate that someone unfamiliar with clinical research in cardiology could gain that impression. It clearly would have been better to add a memorandum to the files at that time indicating my views and the context of the Committee's discussion.

In summary, the information supporting the safety and effectiveness of propranolol for the treatment of patients with moderate or severe angina pectoris is as follows:

1. The medical literature contains 13 adequate well-controlled clinical trials which meet the requirements of 21 CFR 130.12 and nine additional trials with only minor deficiencies. Twenty of these 22 adequate and well-controlled trials support the safety and effectiveness of propranolol for short term use.

2. Widespread usage of the drug for angina pectoris during the past several years in both the United States and abroad has revealed that the incidence of congestive heart failure is not as common nor as difficult to treat as was once feared.

3. The labeling of the drug for use in patients with angina meets a high standard of excellence and is supported by adequate and well-controlled trials relating to short term use and by the informed judgment of qualified experts.

4. Clinical trials are in progress to document further the safety and effectiveness of propranolol in the long term management of patients with angina pectoris. We are prepared to modify the indication in any way depending upon the results of these trials or any other new information which may come to light.

5. There are a large number of additional uncontrolled studies which qualify as supporting evidence for this indication.

J. Richard Crout, M.D.

Appendix A: Propranolol in Agina Pectoris

I. Studies considered as meeting the standards of 21 CFR 130.12

No.	Firm's No.	Reference
1	3	Keelan, Brit. M.J., 1:897, 1965
2	5	Ginn, JAMA, 198:1214, 1966
3	6	Grant, Am. J. Card., 18:361, 1966
4.	11	Gianelly, Ann. Int. Med., 67:1216, 1967
5	12	Harley, CMAJ, 99:527, 1968
6	15	Sandler, Brit, Med. J., 3:224, 1968
7	18	Aronow, NEJM, 280:847, 1969
8	19	Battock, Circ., 39:157, 1969
9	23	Goldbarg, Circ., 40:847, 1969
10	24	Mizgala, CMAJ., 100:756, 1969
11	26	Zsoter, Arch. Int. Med., 124:584, 1969
12	28	Sandler, Clayton, Brit. M. J., 2:399, 1970

13	31	Prichard, Brit. Heart J. 33:473, 1971

II. Studies considered as having only minor deviation from the regulation

No.	Firm's No.	Reference
14	1	Srivastava, Brit. M.J., 2:724, 1964
15	2	Gillam, Brit. M.J., 2:337, 1965
16	4	Gillam, Am. J. Card., 18:366, 1966
17	8	Rabkin, Am. J. Card., 18:370, 1966
18	16	Shafquat, J. Parisian. Med. Ass., 18:117, 1968
19	20	Chhetri, Indian Heart J., 21:273, 1969
20	27	Hvidt, Int. J. Clin. Ph., 3:50, 1969
21	29	Seah, Far East M. J. 6:117, 1970
22	32	Prichard, Postgrad M. J., 47:59, 1971

Dr. CROUT. As Dr. Schmidt points out, there will be, when it eventually gets published, a full congressional hearing record devoted to this issue.

Senator KENNEDY. With your indulgence, Commissioner, Dr. Apter is here. Could she just make a comment on this?

Dr. SCHMIDT. Certainly.

Dr. APTER. Yesterday—day before yesterday, not only did I see the letter written by Dr. Crout, but I also saw the actual transcript of the minutes of the meeting at which the advisory committee considered propranolol. In those minutes several times Dr. Warren and other members said, "We will definitely not recommend propranolol in the use of angina. We will simply, in response to a request from Dr. Crout, specify in what ways it should be used if physicians are using it. We will not recommend it for angina."

I believe that was said at least three times by other advisory committee members, not me, that the decision to put in a recommendation was unanimously rejected. What we voted was to tell physicians who were using it a proper or reasonable way to use it, but certainly not to recommend it.

Senator KENNEDY. That is from the minutes themselves.

Dr. APTER. The actual transcripts, not the minutes but the transcript of the meeting of June 20.

Senator KENNEDY. I want to be accurate here.

This is Dr. Warren: "First of all, we have taken a vote. It came out I think 4 to 1 in favor of recommending the introduction of a statement under the indication segment of the package insert in a qualified way mentioning the use of the drug in angina pectoris. I carefully avoided saying 'recommending the use.'"

That is right out of the transcript.

Dr. SCHMIDT. Mr. Chairman, the subject of the discussion, the decision in the instant case is—does something go on package insert? The drug was approved and on the market.

Now, the issue that was before the Food and Drug Administration was not the putting of the drug on the market, but rather the recognition of its use for this condition on the package insert.

Now, the statement you just read to me about the goals seems to me to be very clear, that the committee voted to put that information on the package insert; that, in effect, was the question.

You do know that much of what is thrown at us is that we do not "approve drugs for certain conditions."

Senator KENNEDY. Did they recommend it for use in angina pectoris? Did they or didn't they?

Dr. CROUT. Well——

Senator KENNEDY. Yes or no?

Dr. CROUT. Yes. And the recommendation was to me. I want to make clear that the Bureau Director is the official to whom the responsibility is delegated for approvals and nonapprovals. So the recommendation is to the Division, and the Division makes a recommendation to me. This is an internal recommendation.

I think there was no confusion about it, in my own mind, as I went over the transcript and studies and it was coupled with our own evaluation of studies, and my own personal evaluation of them.

As I point out, we spent 5 days on this issue in another hearing and you are seeing some of the reasons. We will continue if you like, but there is an open record of the decisionmaking process on that drug.

Senator KENNEDY. Could we get a copy of your letter that refers to this? Did you not sign a letter, Dr. Apter? Was some letter received finally from Dr. Crout?

Dr. APTER. It was the letter of September 4, 1973. I believe it would be with the rest of the transcript materials, and it was my understanding that it says "To Ayerst," that the committee had recommended this drug for use in angina.

Senator KENNEDY. Do you have a copy of that?

Dr. CROUT. Not with me. I would be glad to—I assume Dr. Apter is referring to the approval letter we sent.

Senator KENNEDY. We can get a copy of that?

Dr. CROUT. Fine.

[The material referred to follows:]

FDA APPROVAL OF PROPRANOLOL FOR USE IN ANGINA PECTORIS

Attached are copies of two September 24, 1973 letters from Dr. Crout to Ayerst Laboratories in which notice is given of approval for use of Inderal (propranolol hydrochloride) in angina pectoris.

These letters do not mention the advisory committee's recommendation. We can find no other letters in our files to Ayerst Laboratories of any date discussing the action of the Advisory Committee.

An FDA Drug Bulletin does discuss the approval of use of propranolol and does mention the advisory committee. A copy is attached.

Ayerst Laboratories
Division of American Home Products
Attention: Henry S. Perdue, Ph.D.
685 Third Avenue
New York, New York 10017

4 SEP 1973

Gentlemen:

Reference is made to your supplemental new drug supplements dated June 20, 1973, and July 24, 1973 submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Inderal (propranolol hydrochloride) 10 mg and 40 mg tablets.

Reference is also made to your additional communication dated August 27, 197

The supplemental application provides for a revised package insert to reflec the new indication: "Angina Pectoris Due to Coronary Atherosclerosis".

We have completed review of the supplemental applications. The changes proposed in the supplements are approved.

Sincerely yours,

J. Richard Crout, M.D.
Acting Director
Bureau of Drugs

SEP 4 1973

Ayerst Laboratories
Division of American Home Products
Attention: Henry S. Perdue, Ph.D.
685 Third Avenue
New York, New York 10017

Gentlemen:

Reference is made to your new drug application dated April 4, 1968 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "Inderal (propranolol hydrochloride) Tablets."

Reference is also made to your additional submissions dated June 19, 22, 1973, July 19, 1973, August 23, 1973, and the final printed form of the revised package insert (August 1973).

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The enclosures summarize the conditions relating to the approval of the application.

As indicated in your communication of August 23, 1973 you will preclear your advertisements on the use of Inderal in the treatment of angina pectoris. Please submit this in duplicate and send one of the copies directly to the Division of Drug Advertising (BD-330) with a copy of the package insert.

Sincerely yours,

J. Richard Crout, M.D.
Acting Director
Bureau of Drugs

Enclosures

COPY

FDA
January 1974
DRUG BULLETIN

FDA TO CORRECT DIGOXIN PROBLEMS

FDA APPROVES CEA ASSAY KIT FOR CANCER MANAGEMENT, DIAGNOSIS

FDA APPROVES PROPRANOLOL IN ANGINA PECTORIS

WARNING RENEWED ON ERYTHROMYCIN ESTOLATE

FDA TO CORRECT DIGOXIN PROBLEMS

This is to alert health professionals to new and vital information concerning digoxin tablets.

The FDA has determined that some lots of digoxin tablets may provide significantly lower blood levels (i.e., be less bio-available) than other lots because they are less well absorbed. Such lots, therefore, are not therapeutically equivalent to the better absorbed digoxin products.

The discovery of these bioavailability problems has occurred because science has become more sophisticated, rather than because manufacturers have introduced changes. The problem has undoubtedly existed for a long time, but the recent development of good methods for measuring digoxin blood levels has enabled experts to recognize and define it properly.

Considerable research by universities, industry and the FDA over the last two years has resulted in sufficient data to permit steps toward insuring the therapeutic equivalency of all digoxin tablets. The first step was the establishment by the United States Pharmacopeia on November 15, 1973, of a new compendial standard for the dissolution of digoxin tablets. FDA studies have shown that at least 90% of digoxin tablets on the market already meet this standard. The FDA is now initiating recalls, on a lot-by-lot basis, of digoxin tablets currently in the channels of distribution which do not meet these standards. The products withdrawn will be those with dissolution rates so slow that absorption is only 15 to 30% of the better absorbed products. To insure that all tablets will in the future meet the compendial standard, the FDA is also instituting a lot-by-lot certification program for all manufacturers of digoxin.

Tablets of the following manufacturers are not involved in the initial recall:
American Pharmaceutical Co., New York, N.Y.; Burroughs Wellcome, Research Triangle Park, N.C.; Davies Rose Hoyt, Needham, Mass.; Halsey Drug, Brooklyn, N.Y.; Heather Drug, Cherry Hill, N.J.; Ketchum Labs, Amityville, N.Y.; Lederle Labs, Pearl River, N.Y.; Park Labs, Fredonia, Wis.; Philips Roxane Labs., Columbus, Ohio; Rondex Labs., Guttenberg, N.J.; Strong Cobb Arner (ICN Pharmaceuticals), Cincinnati, Ohio; Tablicaps, Franklinville, N.J.; Towne, Paulsen, Monrovia, Calif.; Vita-Fore Products, Ozone Park, N.Y.; Vitarine (Bryant Pharm.), Springfield Gardens, N.Y.; West-Ward, Inc. Bronx, N.Y.; Zenith Labs, Northvale, N.J.

As a consequence of the present FDA program:

1. All marketed digoxin products will henceforth meet the new USP compendial standards for dissolution.
2. Patients now taking a product with low bioavailability will, at the next refill of their prescription, receive tablets of greater (normal) bioavailability.
Such Patients, (about 10% of those receiving digoxin) have an increased risk of developing digoxin intoxication. Signs or symptoms of intoxication, if they are to occur, should develop within 1-2 weeks after the change to new tablets.
Patients receiving above average daily doses (more than 0.25 to 0.5 mg/day) of the low bioavailability products are particularly at risk. Pharmacists and physicians are urged to reevaluate the digoxin dosage in such patients.
3. Patients receiving digoxin products not subject to recall (about 90% of all tablets) are not at increased risk and no special precautions are necessary. During this transitional period of drug recall, pharmacists are encouraged to keep a record of the lot number and brand of digoxin tablets dispensed as a source of information for the physician.
To assist health professionals the FDA is also establishing an information service in each of its District Offices. As further analyses are carried out, the list of products subject to recall may change; current information on the recall status of each lot from each manufacturer will be available through this service. Pharmacists may contact their State Boards of Pharmacy as well for further information.

It should be pointed out that the FDA, at this time, has preliminary information that *digitoxin* is not necessarily free of bioavailability problems. Studies on this drug are being pursued. Switching of patients from digoxin to digitoxin (or digitalis leaf) merely to avoid bioavailability problems is not recommended. Further information, as it becomes available, will be brought to your attention.

FDA APPROVES CEA ASSAY KIT FOR CANCER MANAGEMENT, DIAGNOSIS

The Food and Drug Administration has issued a license to Hoffmann - La Roche, Inc. to market a radioimmunoassay for carcinoembryonic antigen (CEA). The assay is intended for use in the laboratory as an adjunct to established medical procedures for the management and diagnosis of cancer.

The assay is a complex technique to quantitate the level of CEA in blood. It is capable of measuring nanogram (ng) (1 billionth of a gram) amounts of CEA. The reagents for the CEA assay are to be marketed as a kit and are the first biological substances in the category of *in vitro* cancer diagnostic products to be approved by FDA's Bureau of Biologics.

License applications for other similar types of

CEA-Roche
(carcinoembryonic antigen assay)

	(No.)	0-2.5 ng/ml	2.6-5.0 ng/ml	5.1-10 ng/ml	>10 ng/ml
Healthy Subjects					
Nonsmokers	(892)	97%	3%	0%	0%
Former smokers	(235)	93%	5%	1%	1%
Smokers	(620)	81%	15%	3%	1%
Colorectal Carcinoma	(544)	28%	23%	14%	35%
Pulmonary Carcinoma	(181)	24%	25%	25%	26%
Pancreatic Carcinoma	(55)	9%	31%	25%	35%
Gastric Carcinoma	(79)	39%	32%	10%	19%
Breast Carcinoma	(125)	53%	20%	13%	14%
Other Carcinoma	(343)	51%	28%	12%	9%
Noncarcinoma Malignancy	(228)	60%	30%	8%	2%
Nonmalignant Disease					
Benign-Breast Disease	(115)	85%	11%	4%	0%
Rectal Polyps	(90)	81%	15%	3%	1%
Cholecystitis	(39)	77%	17%	5%	1%
Severe Alcoholic Cirrhosis	(120)	29%	44%	25%	2%
Active Ulcerative Colitis	(146)	69%	18%	8%	5%
Pulmonary Emphysema	(49)	43%	37%	16%	4%

blood assay procedures that may be useful in cancer detection and management are being evaluated.

Prior to FDA approval of the CEA Assay procedure the firm carried out extensive studies which involved examination of over 10,000 subjects by investigators at more than 100 leading medical centers and research institutions in the United States, England and Canada. (A portion of the study data is reproduced in the accompanying table.) Results obtained were consistent with the findings of other investigations, including those conducted by the National Cancer Institute.

These studies show that an assay for CEA in the blood can be useful for monitoring some patients previously treated for cancer for signs of recurrence. The assay may also aid in the diagnosis of certain types of cancers.

The limitations of the procedure as stipulated in the FDA-approved package insert are as follows:

IT IS NOT RECOMMENDED AS A SCREEN TO DETECT CANCER. CEA TITERS ARE NOT AN ABSOLUTE TEST FOR MALIGNANCY, NOR FOR A SPECIFIC TYPE OF MALIGNANCY. IN THE DIAGNOSIS AND MANAGEMENT OF PATIENTS SUSPECTED OR KNOWN TO HAVE CANCER, ALL OTHER TESTS AND PROCEDURES MUST CONTINUE TO BE GIVEN EMPHASIS. CEA TITERS LESS THAN 2.5 ng/ml. ARE NOT PROOF OF ABSENCE OF MALIGNANT DISEASE.

For more detailed information read the full package insert. Additional educational material will be provided by the manufacturer.

FDA APPROVES PROPRANOLOL IN ANGINA PECTORIS

The FDA has approved the use of propranolol in angina pectoris. Because of concern on the part of many physicians that this indication could have been approved some time ago, the sequence of events leading to approval may be of interest.

In 1970, the FDA's Cardiovascular Drug Advisory Committee reviewed data submitted in support of this indication and recommended non-approval. This judgement was based on a relatively high incidence of congestive heart failure in the trials reported at that time and on insufficient evidence of efficacy.

Clinical trials to establish the long-term safety of propranolol in patients with angina pectoris were then begun by the drug sponsor. While these trials are not yet complete, it has become apparent that congestive heart failure is not as common as earlier clinical trials had indicated. In view of this finding and the accumulating evidence of efficacy from well-controlled studies, the FDA's Cardiovascular Drug Advisory Committee has now recommended approval and the Agency has accepted the recommendation.

Consequently, the package insert has been revised to state that propranolol is indicated in selected patients with moderate to severe angina pectoris who have not responded to conventional measures such as weight control, reasonable restriction of activity, cessation of smoking, and use of sublingual nitroglycerin.

Propranolol appears to decrease anginal pain by decreasing cardiac work and oxygen consumption, but these benefits must be weighed against its tendency to increase the left ventricular end diastolic volume. Propranolol should be used with great caution in patients with a history of heart failure or evidence of cardiac enlargement. Concomitant use of cardiac glycosides and/or diuretics may be necessary in such patients.

In any patient the drug should not be continued unless there is a clear increase in exercise tolerance or decrease in anginal pain.

Propranolol should not be used as initial treatment, when angina occurs only with considerable

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20852

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HEW 393

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FIRST CLASS

Important prescribing information from
Alexander M. Schmidt, M.D.
Commissioner of Food and Drugs

FDA January 1974

DRUG BULLETIN

FDA DRUG BULLETIN

News and Reports of Interest to Practicing Physicians and Other Health Professionals, Issued by the Food and Drug Administration, Department of Health, Education, and Welfare. Comments are invited. All correspondence should be addressed to the Assistant to the Director for Medical Communications, Bureau of Drugs, BD-40, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20852.

exercise, or when angina is provoked only by situations which occur infrequently.

The drug is contraindicated in patients with bronchial asthma, sinus bradycardia, second or third degree A-V block, or overt heart failure.

Because there is no simple correlation between dose or plasma level and therapeutic effect, treatment requires careful titration and individualization of dosage.

WARNING RENEWED ON ERYTHROMYCIN ESTOLATE

The toxicity of all erythromycins has recently been reevaluated by the FDA and its Anti-infective Agents Advisory Committee. As a result of this reevaluation, the FDA reaffirms to physicians the fact that erythromycin estolate (ilosone) involves a definite risk of hepatotoxicity (cholestatic hepatitis). Of the several available derivatives of erythromycin, the estolate appears to be the only one that is a hepatotoxic. The hepatotoxicity occurs almost exclusively in adults.

The Committee also determined that the erythromycins differ in absorption characteristics and, therefore, in serum and tissue levels achieved with the same dose. Erythromycin estolate, while carrying the risk of greater toxicity, is on the average more fully absorbed and produces more consistent serum levels than other erythromycin salts and erythromycin base.

The second edition of *AMA Drug Evaluations* contains the following statement:

> "Erythromycin estolate, the lauryl sulfate salt of the propionyl ester of erythromycin, is the only erythromycin ester associated with hepatotoxicity. It can produce jaundice. This reaction is observed most frequently in patients who have previously received the drug but also may occur in those receiving long-term therapy (10 days or more). The jaundice appears to be a hypersensitivity reaction and is reversible when erythromycin estolate is discontinued. There may be accompanying right upper quadrant colic and hepatic enzyme changes suggesting choledocholithiasis. Other erythromycin preparations should be used in preference to the estolate salt in patients with preexisting liver disease or in those suspected of having impaired liver function."

The package insert for erythromycin estolate has been revised to include a box warning of the hepatotoxic potential of the drug. Because this adverse effect is much more common in adults, use of the drug in adults should be limited to situations in which it is clearly justified.

Senator KENNEDY. Thank you very much, Dr. Apter.

I have not seen the September 4th letter, but it certainly seems to me to support exactly what Dr. Apter has stated. It is just their bare lack of volume.

Was that a closed meeting?

Dr. CROUT. That portion was closed, yes.

Senator KENNEDY. Why was that?

Dr. CROUT. I would have to refer to Mr. Vodra for the section under the law, but it was closed under one of the sections of the Federal Advisory Committee Act, which we use to close portions of meetings when decisions relating to approvals or nonapprovals are under discussion.

Premature public disclosure of regulatory recommendations sometimes is not in the interest of the public, and when we make that judgment, we close that portion of the meeting. We close it also when privileged information is under discussion. Those are the only two reasons a portion of the meeting is closed.

Senator KENNEDY. Why is it not in the public interest to have those open?

What public interest is better served by not having open meetings? Trade secrets are not being talked about?

Dr. CROUT. Let me answer the question by saying today that portion of the meeting would be open.

Mr. VODRA. As far as the law goes, well, no. The Advisory Committee Act refers to the Freedom of Information Act for authority in closing meetings. Our interpretation, widely held in various agencies, is that intraagency memorandum discussing policy recommendations and policy alternatives being made to the decisionmaker, in this case, the Director of the Bureau of Drugs, are exempt from disclosure under the Freedom of Information Act and consequently the meetings leading to such memoranda are also closed on that basis.

We generally try to open the meetings as widely as possible, but we do allow for free discussions among the advisors, to discuss the alternatives that are available, before they take a vote on those alternatives.

Senator KENNEDY. What change in the law has occurred that would make them open today where they were closed before?

Dr. SCHMIDT. The Freedom of Information Law specifies under what conditions a meeting may be closed. It does not specify it must be closed.

We have the discretion to open meetings.

I believe the record is quite clear and the evidence is quite plain that the Food and Drug Administration in the last year or so has increasingly become an open agency. Dr. Crout just said the portion of that meeting would be open, whereas before it was not.

We are opening files; we are providing information.

At times we are going to companies and asking them to allow us to release trade secret information in the interest of public information and openness of the agency.

Senator KENNEDY. Are all the advisory committee meetings open where trade secrets are not being discussed?

Dr. SCHMIDT. Right now all of the meetings have an open portion and then generally are closed when trade secret information or regulatory matters are discussed.

Very often there is no request for anyone from the outside to come and nobody from the outside is there, and then really the issue of openness is moot.

Senator KENNEDY. I am trying to find out what public interest is served other than the protection of the trade information, trade secret information. What regulatory matters I think is the way you used it. You said trade secrets or regulatory matters, therefore it is closed.

But outside the trade secret matters, what public interest is served by having those meetings closed?

Dr. SCHMIDT. We are adopting a policy that all meetings will be open except those that discuss matters that are to be kept confidential by law and a few other areas at my discretion, which would include as an example a discussion by agency officials of a regulatory stance that might impact heavily on the stock market. Certainly it would not serve the public interest for some discussions about some matters that are not trade secrets, but are regulatory matters to become the subject of speculation, and so on.

Senator KENNEDY. What matters would be so momentous that they would have such an impact on the stock market?

Dr. SCHMIDT. Well, certainly discussions of alternatives for the requirements, for demonstration of safety and efficacy of the law. Our regulations specify what must be done, what the criteria and standards are.

Senator KENNEDY. Right.

Dr. SCHMIDT. Tough stance versus something else.

We have seen much speculation about Alka Seltzer recently, with fluctuation of the morale of Miles. That is a concrete example, I suppose.

Senator KENNEDY. Can't the stock market not stand the kind of discussions that would take place about questions of efficacy or safety on a particular drug?

Dr. SCHMIDT. Well, it is my decision, and it will remain that, sensitive regulatory matters that are in a stage of discussion wherein we are exploring alternatives will remain a matter within the agency. We have no way of knowing which way something could go, and no useful public good would be served by discussion of these alternatives. That is in my opinion entirely appropriate.

I would like to remind the committee that our new freedom of information regulations go far toward opening up the agency. We have been publishing in the Federal Register procedural regulations that specify how we go about doing our business and how the public, how anyone can have access to the agency and communicate with the agency. These are terribly important and are on the record.

We are otherwise establishing policies for the keeping of minutes, tape recordings, and other records. A prime example of my difficulty with some of the things you read just a minute ago is that a policy was being established by the Bureau of Drugs for the destruction of tape recordings. Now, that was a discussion that was held, I believe, prior to my becoming Commissioner, prior to Dr. Crout's becoming Director of Bureau of Drugs. And we would like to state now the policy is that none will be destroyed, and we have destroyed none.

So that is an error. That also has been the subject to a hearing and there is ample public record on that particular memorandum.

Senator KENNEDY. Do you have copies of memoranda that you sent around to the various departments indicating that?

Dr. SCHMIDT. There is Bureau policy explicit at this point. I believe we have——

Dr. CROUT. That memorandum that you read was not really a memorandum. It was notes of meetings. It was never implemented.

Senator KENNEDY. Sorry.

Dr. CROUT. That was a——

Senator KENNEDY. It says "memorandum" at the top.

Dr. CROUT. That did not initiate policy is what I am saying. That policy in those notes was never initiated. It is an error.

Senator KENNEDY. You mean it was sent out and then not implemented?

Dr. CROUT. It was not sent around the Bureau. It was never sent around the agency.

Senator KENNEDY. Well, it says the Bureau had adopted the policy of destroying verbatim transcripts.

Dr. CROUT. That is an error. We never did so, and do not—never issued a directive to that effect.

Senator KENNEDY. Why would Mr. Brisson write that?

Dr. CROUT. Well, I think you might appreciate the possibility of errors, mistakes.

Senator KENNEDY. Do you have any memorandum that have gone to any of the agencies that set out different policies, either that you talk about or that the Commissioner has talked about.

Dr. CROUT. No, we have a policy that we will maintain the records. That has always been the policy and that is what it is now. Whether or not there is a Bureau directive to that effect, I do not know. There is a verbal one from me to our committee management office.

Senator KENNEDY. You say it is a policy and the Commissioner says it is policy, but it is certainly not being followed in the examples we heard from testimony yesterday.

Dr. CROUT. It is being followed. You have no knowledge of specific examples that I am aware of of destruction of tapes of advisory committee meetings.

Senator KENNEDY. I know the witnesses did. They spoke about it. And you have not presented any evidence here nor has the Commission that rebuts that, except that you say it is not happening.

Mr. VODRA. Would you like us to deliver the transcripts of all the advisory committees?

Senator KENNEDY. I would like the minutes of any briefings of any agency people stating it is policy. Can you supply that?

Dr. SCHMIDT. Yes, sir, I can supply minutes of meetings and a memorandum subsequent to the discovery of that particular memorandum.

[The material referred to follows:]

FDA POLICY CONCERNING RETENTION OF TRANSCRIPTS

OF ADVISORY COMMITTEE MEETINGS

The appended documents provide background information concerning the Food and Drug Administration's policy with respect to the retention of transcripts by advisory committees and indicate the Agency's policy that transcripts of committee meetings shall not be destroyed.

The Food and Drug Administration fully agrees that FDA advisory committees, as well as Agency employees, should be provided comprehensive and written guidance as to FDA policy on development of minutes for advisory committees, recording methods used for committee sessions, and retention of records. This has been one of the Agency's objectives in its procedural regulations which the Agency has been developing for some time. These regulations required a number of decisions by FDA's Policy Board, which consists of top Agency officials, and a proposal will soon be published for comment in the Federal Register. To provide interim guidance pending promulgation of the procedural regulations, the Commissioner had issued a memorandum to all employees and to all FDA advisory committees regarding FDA policy concerning retention of transcripts.

The appended documents are as follows:

1. October 29, 1974 memorandum from Director, Executive Secretariat to Commissioner explaining the memorandum titled "Minutes of the Commissioner's Staff Meeting with the Bureau of Drugs, 11/30/72," dated December 1, 1972.

2. Excerpt from transcript of January 31, 1974 meeting of the OTC Panel on Topical Analgesics, which is representative of presentations made to OTC Panels.

3. January 27, 1973 memorandum from Peter Barton Hutt, Assistant General Counsel, Food and Drug Division to Gary L. Yingling, Director, OTC Drug Review.

4. September 25, 1973 memorandum from Chairman, OTC Review Steering Committee to Panel Members, OTC Drug Review Program regarding, inter alia, records of panel meetings.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : The Commissioner

DATE: October 29, 1974

FROM : Director, Executive Secretariat (HF-1)

SUBJECT: Clarification for the Record; Minutes of the Commissioner's Staff Meeting with the Bureau of Drugs, November 30, 1972

1. This is in response to your request for a clarification of item number three of the minutes of the above-referenced staff meeting. These minutes state that the Bureau of Drugs had adopted a policy of destroying verbatim transcripts of advisory committee meetings as soon as minutes had been approved by the committees.

2. I have discussed this with various staff people associated with committee management and have determined that no written directive was ever issued, either by the Commissioner or the Director of the Bureau of Drugs, which called for the destruction of verbatim transcripts following approval of the minutes of standing advisory committees. This policy was being actively considered but was subsequently rejected. I must, therefore, conclude that I must have misinterpreted the remarks made at the November 30, 1972 meeting; and that the statement in the minutes of that meeting is in error.

3. There were, however, decisions made in this subject area with respect to the expert panels conducting the over-the-counter (OTC) drug review; and the following chronology is offered for the record.

- In May 1972, when we were preparing to initiate the OTC review, there were discussions at the Commissioner's Staff level regarding the confidentiality of OTC panel transcripts and whether these panels should be given the option of editing or destroying transcripts after the panels had concluded their deliberations and submitted the OTC drug monographs.

- In June 1972, a decision was made by the committee overseeing the OTC review project to permit the destruction of transcripts, if any, once the minutes of the meetings had been prepared and approved by the panels.

- In July 1972, that decision, which had in fact not been carried out (only two or three panels were in existence at the time), was revised; and a policy was adopted that called for the destruction of panel transcripts only after each panel monograph had been prepared and submitted. The OTC review panels were so advised.

- In January 1973, a California attorney (Mr. Van Smart) filed a suit against FDA under the Freedom of Information Act, requesting transcripts and minutes of closed portions of certain OTC panel meetings. On January 27, 1973, Peter Barton Hutt, Assistant General Counsel for Food and Drugs, advised Gary L. Yingling, Director of the OTC Drug Review, that in view of this lawsuit it would be improper for any transcripts to be destroyed until the lawsuit was resolved. (The suit was decided in favor of the Government in April 1974.)

- In May 1973, review panels were advised that the decision to provide for verbatim transcripts of closed portions of their meetings would be left to the respective panels. They were also advised that, in view of the pending litigation (Van Smart case), FDA could not assure the confidentiality of these transcripts.

- In a September 25, 1973 memorandum to each OTC panel member, Dr. John Moxley, Chairman of the OTC Review Steering Committee, pointed out available alternative means of recordkeeping and the disposition of such records (copy attached).

4. Presently, the decision regarding what means may be utilized for keeping records of panel meetings is still left to the individual panels. All panels, however, have been advised that no tape recordings or transcripts may be destroyed pending a specific policy decision by the Commissioner. Insofar as standing technical advisory committees are concerned, present policy is to retain any verbatim transcript or tape that may be prepared.

5. I am seeing to it that each recipient of the minutes of the November 30, 1972 meeting gets a copy of this memorandum.

E. L. Brisson

Ernest L. Brisson

Enclosure

Topical Analgesics Panel 1/31/7

whether that stays as it is, or is replaced, or what?

MS. GEISMAR: We finished it off yesterday.

DR. KANTOR: There is some talk about camphor and phenol.

COL. AKERS: Phenol is going to be today, though.

DR. KANTOR: Yes, so it is only part of page 13. We really did not prepare phenol at that point, which is going to be presented today and we could leave it out of that, completely, and just forget about all of page 13.

MS. GEISMAR: That is what I thought that we would do.

DR. KANTOR: We have Mr. Scarlet here with his little talk and we are already 15 minutes into his time. I am sorry.

MR. SCARLET: I am a lawyer with the Office of the General Counsel and Gary Yingling has asked me to appear at the various OTC panel meetings to discuss the question of transcripts and tape recording of the panel operations.

The reason for my appearance here is the pending litigation, which is entitled Smart versus the Food and Drug Administration, in the California District Court and to give you a little background. I will just describe what the case involves.

Van Smart, who is the plaintiff in the lawsuit, was once employed with the Food and Drug Administration in the Compliance Division of the Bureau of Drugs, I think, if not the Compliance Division of the Food and Drug Administration itself. When he left the agency, he went into nominal private practice in

California, retired, I gather. He has quite a lot of background in both the substance of FDA's activities and in the law which applied to both the substance of activities and the releasing of information by the agency.

In mid 1972, shortly after the OTC review initially got underway, Mr. Smart requested a lot of documents concerning the Antacid Panel. At that time, many of the documents which he requested were not being made available. This included submissions to the Antacid Panel. It included, I think, the minutes kept by the Antacid Panel and it included the transcripts maintained by the Antacid Panel.

I think the policy today is different with respect to minutes. Submissions to the panel, I gather, are still kept confidential until the panel makes it recommendation. The transcripts are still not released.

In any event, Smart's request was turned down as to most of the documents which he requested. He appealed that decision and that decision was affirmed and then he filed suit in January of 1973. While the suit was taking its course, the Antacid Panel was taking its course and as a result of the normal operation of othe OTC review procedures quite a bit of the information which Smart requested concerning the Antacid Panel was released to him. However, the transcripts never were and probably the main bone of contention is going to boil down to the transcripts.

After Smart filed his complaint he engaged in some discovery with the agency, including interrogatories and requests for productive documents. With each item of discovery he expanded his scope of inquiry to some extent. He did not amend his complaint, but he gradually started picking up other panels, such as the Dentrifrice Panel, the Antimicrobial Panel, and maybe one or two others, in his requests for discovery.

The suits has not yet reached even the pre-trial stage. It is still in the discovery phase, but as a result of the suit some deicsions have been made by the agency with respect to transcripts.

As you know, the decision whether or not to maintain verbatim transcripts, whether on tape of transcribed, is made solely by the panel. Until now, the position of the agency defended the fate of any verbatim transcripts was also within the panel. This is no longer the case. If the panel decides to keep verbatim transcripts, they will be retained by the agency and will not be disposed of. They will not be released, either, except under court decisions. They will also not be relied upon by the agency. The agency has not ever, to anybody's knowledge, referred to the verbatim transcripts kept by any panel for any purpose and will not do so and, therefore, any transcripts that are retained by the agency will be retained in their raw form. If they are on tape, they will stay on tape. If they are in written form, they will stay in unindexed written form, locked

up somewhere.

The reason why they are going to be retained is the obvious provocative impact that destruction of the transcripts would have, given pending litigation, given the pending atmosphere concerning the destruction of documents, but it is still up to the panel whether or not it wants to continue keeping the verbatim transcripts. The transcripts are solely for your use. If you find them useful and recognize the possibility that they may, at some point, be released by the agency required by a court, then of course keep them if you want. If you do not want to keep the verbatim transcripts, you need not.

You do not have to keep them in the first place. If you keep them, they stay in existence.

DR. SHUCK: When you say that we do not have to keep them, what do you mean?

MR. SCARLET: It means that you can turn off the tape recorder and talk. You do not have to keep them.

COL. AKERS: They are not a legal requirement. If you make them, you have to keep them.

DR. SHUCK: That is the question I was trying to find out. Keeping them, I was thinking about recording them and keeping them. By keeping them, you meant recording them.

MR. SCARLET: I mean to retain them. I do not mean to make them. If you transcribe the proceedings, you must retain whatever transcription you have made. The problem, from your

"point of view, obviously, is that if they are released what you say here is going to become public knowledge for whatever effect that may have on you at the time that it becomes publich knowledge or at the time you make the statements, knowing that there is a possibility that the statements may become public. I do not know what your views are on that. I also do not have any recommendation as to whether or not to keep the transcriptions.

DR. KANIG: What if the Panel decides from here on in not to keep transcripts or tapes? What about the ones that have already been prepared?

MR. SCARLET: They will be retained.

DR. KANTOR: Do you have any idea what the motives of Smart are?

MR. SCARLET: Mr. Smart was present in the Agency during the time of a reshuffling, a bureaucratic reshuffling which I understand happens every three or four months, and he felt that he was not well treated. I do not know whether there is any basis for that feeling, but he did leave the Agency with some rancor. That is probably a contributory factor. He may also simply be a person who feels that his time can be profitably spent in exercising an oversight function with respect to FDA activities.

From reading his claim you do not get any clear feeling about whether he is pro or anti anything in particular other than FDA. There are points. He seems to think that the

FDA is favoring industry, and he seems to think that the FDA is taking action which cannot be justified with respect to the industry. The only thing that clearly emerges is that he thinks that the Agency is acting illegally in keeping the Panel sessions closed and in refusing to permit transcripts of the Panel sessions to be made available to the public.

DR. AKERS: He is representing himself as an individual and not a member?

MR. SCARLET: That is correct. To anybody's knowledge he is not being supported financially or in any other way by any consumer or trade association.

DR. KANTOR: What do you envisage? In other words, what could he do? What potential is there? Let us say that he were given the transcripts. Then what?

MR. SCARLET: What the transcripts would be useful for would be any attempt to discredit the Panel's recommendations, and this is one reason why the transcripts are not made available. Obviously what you say here bears a relationship to what finally comes out from the Panel, but whether it bears a clearcut relationship or a very tenuous relationship is another matter.

Things you say here do not necessarily reflect what the ultimate decision is. You can discuss something here and then sort of talk among yourselves in the evening or at lunch and then sort of reconsider things and munch over them and

come back here tomorrow and say something completely different. Somebody would then take a transcript from today and a transcript from tomorrow and say, "Good God, these people are inconsistent, arbitrary, capricious and acting illegally." Somebody could bring that into court and say, "As reflected in the verbatim transcripts of the Committee proceedings the Committee did not know what it was doing, and furthermore it was inconsistent, and not only that but it had a lot of irrelevant, trivial, slanderous things," if that is what you have been saying. I do not know.

MS. BERRY: What are the chances of the FDA retaining control of the transcripts under intra-agency exception under the Freedom of Information Act?

MR. SCARLET: I think there is a fairly good chance of invoking that exemption. That to me at least, is the most important exemption, and unlike most --

MS. BERRY: It would apply to discovering.

MR. SCARLET: Yes, it would, and unlike most situations in which federal agencies invoke exemptions, in this case I think it is justified. Usually they invoke them just because they do not want to give it up, whatever it is that is being requested, but here is a clear example where you are dealing with internal deliberations of policy orientation. The cases that I have read hold that, for example, take the FCC. When the FCC issues an order, that must be made publicly available.

Anything similar to an order like that must be made publicly available, but the internal documentation which supports that decision is not publicly available, and here I think you have an even stronger case, because viewing the situation analogously the thing which is of ultimate concern is the final monograph which the Commissioner signs. The cases would say, I think, that internal memoranda directed to that final monograph would be non-disclosable under most circumstances. The Panel deliberations here are even farther back in the chain because they concern only the underlying reasoning of the Panel in proposing a monograph, and the transcripts are not relied upon by the Commissioner himself. So, you are even farther away from the thing that you are actually concerned with. So, I think it is clearly non-disclosable as an internal policy document.

However, there are certain legal problems which I will not belabor, but suffice it to say that the presence in these deliberations of consumer and industry representatives raises problems, not insuperable problems, but problems.

I think that we will probably win the lawsuit, but there is no guarantee.

DR. KANTOR: What would be our situation. Let us just say that he wins and he gets the transcripts, and he does make them public in some context. What practical thing could we do as individuals? Could we sue him and on what grounds?

MR. SCARLET: No, the only thing to do is to respond,

and if he takes things out of context, give the context and if there is a context beyond the transcript itself, give that and explain any particular comment that is made. I do not mean to overemphasize the problem in looking at verbatim transcripts. Any judge who looks at the verbatim transcript is going to recognize it for what it is. Judges are engaged in this sort of thing all the time. Any district judge has been on a three-judge panel, and I can just imagine what they say when they get together and how they would not like what they say to get out either because it would not be an accurate reflection of what they decided, and it is unfair to base anything on comments made in a context like this, and for that reason I think that the transcripts would not have too great an influence on a court if anybody tried to challenge the monograph, if that is what they were being used for, but of course they could always get out into the Times and the Post and have one of those little boxes in the Metro section which says that FDAers say, "Such and such and such and such." It would make life a little bit more difficult.

DR. SHUCK: What use is made of the transcripts at the present time? Who listens or uses them?

DR. KANTOR: The people who make up the minutes need them.

DR. SHUCK: We all take notes here. You are taking notes. So, is it useful in writing the minutes?

MS. GEISMAR: Oh, yes. There is no question about it. Don't make that your prime consideration. The Panel, especially when you are writing your final report, may want to go back and go over an area you discussed to refresh your memory of what you said, because let us face it, neither the minutes nor anything else is going to show exactly what everybody said, you know. You know, it is summarized.

MR. GINGRICH: I think we also get to the point --

MS. GEISMAR: You get a set, too.

MR. GINGRICH: What type of minutes do you want? Do you want the summary type of minutes that you had in the last meeting or do you want narrative minutes?

DR. KANTOR: We have sort of thrashed that out and we have got ourselves somewhat formalized, at least for the next subject, because we are going to be just beating our heads against products, and we have a set format for that with written material. So, it really would not be that much of a problem. However, there are some of these philosophical discussions that we have where we are changing our minds about things as we go along, and one tends to forget sometimes what you have already decided upon in the heat of an exchange.

So, they do have their uses. There is no question about it. Originally we all objected to the idea of tapes because tapes, as one can easily see, can be fussed around with. Written transcripts from tapes which we were assured would be

then destroyed are something else again. At least she has a record.

DR. LANMAN: Will those be destroyed? I mean, are you going to keep the tapes?

DR. KANTOR: No, the tapes have been destroyed.

MR. SCARLET: What is the method of transcription used by this Panel?

DR. KANTOR: It is on tape which is then transcribed into writing, and the tapes are --

MS. GEISMAR: The recording company does this.

MR. SCARLET: As to the recording company, I think we would just allow them to follow their ordinary procedure.

DR. KANTOR: Can they be subpoenaed?

MR. SCARLET: Can the recording service documents be subpoenaed from the recording service? Certainly.

DR. LANMAN: They will keep the tapes for two years.

MR. SCARLET: Don't you keep the transcripts from the recording company?

DR. KANTOR: Yes.

MS. GEISMAR: That is what we keep.

DR. LANMAN: I thought that the recording company also keeps the tapes for two years.

DR. KANTOR: Wait a minute. We asked about that. We asked them to destroy them.

DR. KANIG: The tapes are destroyed but not the

to make minutes, and then he would destroy his own notes.

MR. SCARLET: They discovered on discussion among themselves that the tapes were totally academic because they were not even used to prepare minutes. They were just sort of there, not serving any function in their case. The only possible function that the tapes could have served would have been had the panel members as they were preparing their final recommendation wanted to refer to past committee deliberations for a purpose. Otherwise there apparently was no purpose for the tapes.

DR. KANIG: There was a purpose because Judy Jackson insisted that they keep them. They had not wanted to.

MS. GEISMAR: unmonitored tapes are just about of no value at all. When people start talking together you cannot hear what anybody said or who said it. They are hopeless for getting anything out of it.

DR. KANIG: If anybody wanted to create mischief they could use what is on the tapes.

MS. GEISMAR: No, I mean to the Panel they are almost useless to use as a working tool, tapes alone.

DR. LANMAN: Actually, if anyone wanted to create mischief, they are going to creat it whether you have got them or not. I think using these in order to make minutes is a convenience, and it is a good thing. I certainly in my recollection of what is said here there is nothing that anybody

Gary L. Yingling (BD-109) January 27, 1973

Peter Barton Hutt (GC-1)

OTC Antacid Panel Transcripts

As you know, we have told the OTC panels that all transcripts of their deliberations will be destroyed after the final report is prepared.

In view of the lawsuit filed by Mr. Smart to obtain copies of the transcripts, however, it would now be improper for any of these transcripts to be destroyed until the lawsuit is resolved.

MEMORANDUM

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO: Panel Members, OTC Drug Review Program

DATE: SEP 25 1973

FROM: Chairman, OTC Review Steering Committee

SUBJECT: (1) Literature Searches and Abstracts
(2) Records of Panel Meetings

I would like to bring to the panel members' attention two matters of importance to the OTC Drug Review program that require clarification.

I. Literature Searches and Abstracts

When the OTC Review was conceived over a year ago, the Steering Committee recognized the need for providing panel members with as complete a guide to the relevant scientific literature as could be obtained. The most practical means, it seemed to us, was a search of the literature and the abstracting of relevant scientific articles. The FDA library has done an outstanding job of providing the bibliographies and abstracts for the panels now in operation, but it has been necessary to limit the scope of the searches because of the large numbers of ingredients involved. For that reason, not all labeled active ingredients have been searched nor has it been possible to guarantee that every relevant article is listed.

The bibliographies and abstracts are intended to be a starting point for reviewing the scientific material on the drugs involved. Panel members will no doubt find relevant articles not cited by the FDA library. For example, articles published prior to 1950 have not been included, and the foreign literature has not been searched at all. Articles published in the most recent six-month period are generally not included because that is the time needed for preparation and publication.

Panel members should not feel constrained to limit their review of the literature to materials contained in the FDA literature search nor to limit the review to those ingredients appearing therein. The FDA material is just one of the sources that should be used in carrying out the review.

Such additional material as you may wish to use should be identified and made part of the total data submitted.

II. Records of Panel Meetings

The Steering Committee believes it is essential that summary minutes of each panel meeting be written and made available to those having an interest in them. The summary minutes should reflect the subjects discussed, the substance of the panel's discussions, including presentations by non-members; the panel's interim judgments and citations of evidence in support of them; and if a report is prepared by one or more members of the panel and approved by the panel it should be included as an addendum to the minutes. Ideally, the summary minutes should be maintained in such a manner that at the conclusion of the panel's deliberations, they will contain the substance of a final report.

Obviously, some means of recording the panels' decisions is necessary in order to ensure the accuracy of the minutes. Methods that have been used thus far in the Over-the-Counter Drug Review include the following:

1. Tape-Recording: Some panels have used a tape recorder and microphones set up by the staff at every meeting. The staff personnel keep a log of each tape to make possible the locating of specific information on the tapes. The tapes are provided to the person preparing the summary minutes. After the minutes are approved, the tape may be erased or it may be kept until the report and proposed monograph are transmitted to the Commissioner.

2. Dictating: A second method is to have statements dictated by the panel members to the Executive Secretary. These statements are typed after the meeting and presented to the panel for approval. No verbatim record is kept.

3. Stenographic Transcripts: A third method is to have a stenographic reporter at the meeting to record the entire discussion. The advantage of this method is the ready availability of a written record to aid in the preparation of minutes. A stenographic record cannot be destroyed for a period of two years--the length of time such records are kept by the recording company.

The OTC Staff would be pleased to discuss and answer any questions you may have about these matters.

John Moxley, III, D.

Dr. SCHMIDT. I asked Mr. Brisson to even go about talking to people that were there to see if that policy had been discussed. He could find no reason for himself to have written that sentence, that point in the minutes, and concluded he must have been in error.

Subsequently, in different kinds of committee meetings, the OTC review, and other activities, where tape recordings are kept, and so on, we have issued policy in the presence of and directed to the committee management staff, that the records will be kept that is in the minutes of these meetings.

Senator KENNEDY. Do all your employees know about it?

Dr. SCHMIDT. Well, the point that you made a minute ago about the testimony you received barely 24 hours ago, we do not have. I do not have that testimony in front of me. Nor do we have specific dates and episodes that we can investigate. So that I am at a disadvantage. You have an advantage.

I would like to investigate and will, as I said, with your overseeing if you prefer, each and every concrete allegation. Because I think, one, they are terribly important, and two, since I have been Commissioner, they have not been occurring.

Now, the specific instances that—if my reports are accurate, I don't believe have been occurring recently in conflict with the agency policy that I have strongly stated.

Senator KENNEDY. Doctor, obviously we will make a part of the record any detailed response to those allegations.

I would appreciate it if Dr. Bryant nevertheless updated his summary as requested in his memo April 26, 1974, as though he were willing to accept the published reports as being totally accurate and reflective of raw data. That has happened since you have been there.

Now, either Marion Finkel does not understand what your rules or regulations are, or the people that we heard, the 14 people we listened to yesterday, do not understand those to be the rules.

You have not brought anything to show us here this morning that these regulations have been circularized.

We had sworn testimony from advisory groups to the contrary, that they could not find either guidelines or patterns.

Dr. SCHMIDT. Well, it does nobody or the situation any good to deal with generalities.

I really must——

Senator KENNEDY. These are about as specific as you can get.

Dr. SCHMIDT. Well, I know, but I cannot speak specifically about the things you are asking about because I have hardly had time to look into them, obviously.

Senator KENNEDY. Yes.

Dr. SCHMIDT. And, secondly, there are other alternative explanations which are quite meaningful for at least some of the things you heard yesterday. For example, the memorandum you just read from Dr. Marion Finkel is subject to the differences in nuances of the English language. I have no idea what she meant to convey by that, but I will find out.

Senator KENNEDY. That does not seem to be subject to much difference in interpretation. It seems to me quite clear.

Dr. SCHMIDT. I will have to respond and I will.

[The material was subsequently supplied for the record:]

MEMORANDUM DATED MAY 1974 FROM DR. FINKEL REGARDING DR. BRYANT'S REVIEW OF DATA

To discover what was meant in the subject memorandum, the Commissioner of Food and Drugs requested an accurate, complete, specific and relevant account of the views of both Dr. Finkel and Dr. Bryant concerning this episode and will address the issues involved in the report based on his investigation.

Senator KENNEDY. Doctor, it seems to me that there may very well be explanations for one or two of the circumstances that were brought up in the course of our hearing yesterday, but the fact that we had 14 professional people, many of them very renowned and qualified individuals, all reaching similar conclusions. I would think that you would be spending a good deal more time in trying to remedy the whole situation, rather than just trying to rebut particular individuals, in particular situations.

We had 14 of those individuals; I am informed we could have had 40 of them. These were not that tough to get. [Laughter.]

We do not want to be coming right back in another few weeks with another 14. It seems to me it is going to take more than just oral communication. I mean, it is really going to take a shaking up.

Dr. SCHMIDT. Well, I am a little nonplussed, because I tried to say two things: One is that I will follow through on each and every charge, and in fact you charged me with that publicity.

But the thrust of my comments was to say that our procedures have been changed and are being changed. It is all over the map, what we are doing. The changes are designed exactly to do what you said, to take care of a big problem.

Now, you know, there are over a thousand people in the Bureau of Drugs, obviously, a much more limited number of physicians. I agree with you that it was not hard for you to come up with that list of 14.

Senator KENNEDY. Yes, but how many medical officers? We were very limited in the area. We were just looking for medical officers. How many medical officers do you have, 60 or 70?

Dr. SCHMIDT. About 100.

Dr. CROUT. 80.

Dr. SCHMIDT. About 80.

Senator KENNEDY. Well, we had 8 or 9 of the 80, and as I say, it is not that difficult to come up with more.

We do not want to be spending so much of our staff time just over at FDA, but, this is not that difficult a problem to discover over there.

Dr. SCHMIDT. I agree.

Senator KENNEDY. I am glad you are going to look into this and work with us.

Let me ask this. Will you now record contacts with drug companies, either formal or informal?

Dr. SCHMIDT. Well, in this regard, I did the following: Some 2 or 3 months ago I asked that a study be done of the feasibility of all contacts in the agency being made public. A study was done on the cost of doing it, the accuracy of such a list in the large agency, and so on. That study reached my desk very recently and, as a result, I made only one decision to date, which has been implemented. That is that my own personal calendar will be published weekly with a listing of everyone outside the Federal Government with whom I meet, and the purpose.

There will be minutes kept of each such meeting which will be publicly available, and that is 100 percent.

Now, beyond that, the Policy Board of the Food and Drug Administration, which discusses general agency policy, will, on the basis of this study, make a decision about how far down in the agency we can carry that policy.

Senator KENNEDY. What is going to be your recommendation?

Dr. SCHMIDT. My recommendation will be that it be done through Bureau heads and for all officials of the Office of the Commissioner. But not beyond that.

The reasons for my recommendation are: one, if there are the kinds of meetings that anyone would want to follow, they will most often involve the Bureau Director or one of the persons that I mentioned.

Simply because I expect things to escalate to the management level, if there is a problem.

Second, the study indicates the expense of trying to keep an accurate list of the literally hundreds of meetings of the hundreds of people in the agency, would be prohibitive given our budget and the number of people it would take to do it.

Part of the reason that I may not be able to come in here like other agencies and put a memorandum on the table is that I am insisting that all of our procedures be spelled out in the Federal Register. And in the Federal Register, our procedural regulations will specify that minutes will be kept, and what minutes will be available. These are almost ready for publication but have not been finalized.

Senator KENNEDY. I do not understand why it is too burdensome for anyone, from the top of the Department down through the medical officer who has any contact with a drug company, to make a note of it and put it in the file.

Dr. SCHMIDT. Well, notes, that is now done. What I am talking about is——

Senator KENNEDY. You mean every contact, both formal and informal, is in the files?

Dr. SCHMIDT. Yes, sir. That is policy. That is understood by the people in the agency.

Senator KENNEDY. Where is that policy statement?

Dr. CROUT. That has been long-standing Bureau practice for years. Now, if it is not being well enforced——

Senator KENNEDY. Where is it? How do people understand it, new people coming into the Department? Where do they get their little sheet?

Dr. CROUT. If one comes in, I do not know if there is a memorandum to that effect. I would have to go back into our old files and look.

You have properly and correctly identified that a large number of in-house procedures need to be updated in modern terms, and we have started a Bureau of Drugs Manual revision during the last year. But one proceeds on it slowly.

Part of the reason that we do not—cannot—reassert everything instantly is that we are an institution in transition. So many of our procedures, where things flow or documents flow and so on, are not written down perfectly at the present time.

Policies that you mentioned, though, of memoranda for every phone call and for the contacts are of long standing.

Senator KENNEDY. They are not being carried out?

Dr. CROUT. They will—we will look into that. To my knowledge that is an enforcement problem for our personnel.

Senator KENNEDY. Don't people understand it?

Dr. CROUT. I am not sure that it is being neglected as much as you might think.

Senator KENNEDY. I am not sure it is being carried out as much as you might think. [Laughter.]

Dr. CROUT. Possibly.

[The following information was subsequently supplied for the record:]

FDA POLICY CONCERNING RECORDING OF CONTACTS WITH INDUSTRY

1. Employees of the Food and Drug Administration have long been instructed to prepare memoranda of meetings or phone calls with regulated industry and to see that these memoranda are included in the appropriate files. This is learned as a part of the on-the-job training and is also reflected in the attached excerpts from the old Bureau of Drugs Manual, now undergoing revision, dealing with procedures for investigational new drugs (141.1), new drug applications (243.2), antibiotic drugs (330.1), and "not new" drugs (524.4).

2. Of relevance to this issue is the FDA policy concerning discussions of proposed or final regulations prior to their publication in the Federal Register, which is spelled out in the attached memorandum dated November 2, 1973, from the Commissioner to the Agency's Bureau Directors. This memorandum had as its purpose the protection of the integrity of FDA's rulemaking process through restrictions upon ex parte communications between FDA employees and individuals outside FDA, including representatives of industry.

3. To clarify Agency policy concerning recordkeeping of meetings and conversations with individuals outside the Agency, on September 18, 1974, the Commissioner sent the attached memorandum to all employees. The policy described in the memorandum shall apply pending promulgation of FDA's procedural regulations.

4. Since the August 16 hearing, the FDA Policy Board has reached agreement upon the Open Calendar procedure which was discussed by Commissioner Schmidt. Attached is the memorandum establishing the procedure.

6. Discussions with Sponsor or Others. Any discussions with the sponsor or his representative by telephone or in person are to be described in a memorandum for filing in the IND. Similarly, discussions with others which relate directly to an IND and the conclusion reached or action taken should be described in a memorandum for inclusion in the file.

X Resume of all conferences, contacts with applicant or investigators, outside consultations, inside consultations, expert panels, Drug Surveillance Branch, IND summary, statisticians (Statistical Evaluation Branch, BMI), and comparison and justified contrast with labeling of all related marketed drugs and new drug applications.

4. Inquiries from Industry. Inquiries concerning the manufacture and certification of antibiotic drugs are referred to the Division of Antibiotics and Insulin Certification (BS). Inquiries pertaining to toxicology and clinical studies are referred to the Division of Antibiotic Drugs (Bureau of Medicine). Applicants are encouraged to make all inquiries concerning pending antibiotic applications in writing. When conferences are necessary to discuss the applications, applicants should make appointments in advance. Personnel having contact with an applicant by telephone, conference, or personal visit are required to prepare a memorandum of the discussion. Members of industry should not be informed that a proposed antibiotic regulation has been forwarded to the Office of the Commissioner for final action.

b. Industry Consultation. From time to time members of the Bureau of Medicine meet with representatives of industry together with members of the legal staff serving the Food and Drug Administration and advisory or regulatory bureaus. Manufacturers are also taxpayers and are entitled to our advice and opinions even on matters which seem trivial to us. Remember that any opinions expressed during these conferences will be interpreted as the official opinion of the Food and Drug Administration and may well be disseminated by grapevine to all segments of the industry. If questions arise which cannot be answered on the spot, take time to study and research the matter in question thoroughly and render a definitive opinion in writing at a later date. Opinions establishing new policy and precedent should be cleared at the Bureau level and may require clearance in the Office of the Commissioner or General Counsel. All conferences with industry representatives are required to be written up for the file.

See Below

NOV 02 1973

Commissioner of Food and Drugs

Discussion with Individuals Outside FDA
During the Development of Regulations

The Food and Drug Administration has no formal regulations or guidelines on discussion of proposed or final regulations prior to their publication in the Federal Register. It appears that internal practices vary widely among individuals and Bureaus. I believe that uniform guidelines should be adopted so that we all follow the same general approach. I am therefore suggesting, for your consideration, the general guidelines set out below. This will be the subject of further consideration at one of our Policy Board meetings, after which I will promulgate final guidelines for the Agency.

1. All FDA employees should be free to solicit ideas and recommendations for regulations from any interested individual or organization. We obviously have expertise in the areas in which we regulate, but we certainly do not have exclusive rights on all creative ideas and approaches. Any source of assistance in developing new concepts should therefore be welcomed.

2. Once we have decided to prepare a proposed regulation, it is expected that the general concepts may well be discussed, in general terms, with any number of interested individuals and organizations. At no time, however, will a draft of the regulation (or any portion thereof) be furnished to any individual or organization, and at no time will explicit details of the proposal be discussed with any individual or organization. The only exception is when specific permission for such discussion has been obtained from the Associate Commissioner for Compliance and from the General Counsel. These two individuals have particular responsibility for regulations and are in the best position to judge the impact that release or discussion of detailed information may have upon the Agency. Ordinarily, release of such detailed information will be permitted only where it is furnished to all representative groups, including, for example, consumers as well as industry representatives.

3. Once a proposed regulation is published in the Federal Register, and before a final order is prepared, discussion of the proposal with all interested persons is to be encouraged. It is obviously helpful to understand questions raised about the proposal, and concerns expressed about it, so that the best possible final regulation can be developed.

4. In preparing the final regulation and its preamble, even more stringent rules apply than when preparing the proposal. Ordinarily, a copy of any draft of a final regulation will not be furnished to any person outside FDA, and details will not be discussed. The furnishing of a copy or discussion of details is again to be permitted only with the consent of the Associate Commissioner for Compliance and the General Counsel; such consent will be provided only under rare circumstances. The integrity of the regulatory process requires that a final regulation be prepared internally, on the basis of the public administrative record (i.e., the comments and other documents on file with the Hearing Clerk), and not on the basis of ex parte communications. If any technical assistance is necessary at this point, it should be furnished in the form of written communications to the Hearing Clerk. In the event that direct discussion of a draft document is required, we will devise appropriate protective procedures (such as the "tentative final order" filed with the Hearing Clerk for low-acid canned foods) to make certain that our obligation to develop a full and impartial administrative record is met.

5. Once a final regulation is published in the Federal Register, there is again no prohibition against any form of discussion, except where the regulation is subject to formal objections and a request for a public hearing. In this latter situation the law requires careful consideration of any ex parte communications both during the 30 days when objections may be filed and after any such objections are in fact filed. Accordingly, in these situations, there may be no discussions whatever with persons outside FDA except with the concurrence of the Associate Commissioner for Compliance and the General Counsel.

A. M. Schmidt.

Alexander M. Schmidt, M.D.

Addressees:
Director, Bureau of Drugs
Director, Bureau of Foods
Director, Bureau of Biologics
Director, Bureau of Radiological Health
Director, Bureau of Veterinary Medicine
Director, Office of Medical Devices

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : All FDA Employees

DATE: September 18, 1974

FROM : The Commissioner

SUBJECT: Memoranda of Meetings (including telephone conversations)

The FDA Policy Board has been considering new FDA administrative procedures since last fall. Proposed regulations will be published in the Federal Register this fall. In the interim, I am releasing some of our conclusions for immediate implementation.

As a result of my expressed commitments to maintain the integrity of the regulatory processes of this Agency and to promote openness in Government, I am hereby reaffirming, as written policy, the long-standing practice of preparing memoranda of important meetings (including telephone conversations) between FDA personnel and persons outside the Federal Government.

Memoranda of meetings (including telephone conversations) held between employees of the Food and Drug Administration and persons outside the Federal Government involving an important matter, a decision or an issue, or statements or advice or conclusions to which future reference may be required as part of the administrative record, will be promptly written and become part of the official files.

These memoranda will be publicly available upon request, except for those which fall under the exemptions provided in the Freedom of Information Act and regulations, or which contain information prohibited from disclosure by existing statutes.

In each case, these memoranda are to contain the following information:

a. Date of meeting or conversation;

b. Names of participants and affiliations;

c. Location of meeting;

d. Statement of subject matter discussed, including any conclusions, decisions, agreements, or follow-up actions.

Memoranda are to be brief and concise. Discussions, arguments, etc., are not required to be included, only the final actions.

All memoranda which relate to any petition or regulation formally pending before the Agency shall promptly be filed with the Hearing Clerk and made a part of the public administrative record of the proceeding.

Adherence to this policy should result in more complete records and information so necessary in making sound decisions and promote public confidence in our regulatory activities.

A. M. Schmidt.

Alexander M. Schmidt, M.D.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : See below

DATE: OCT 29 1974

FROM : Commissioner of Food and Drugs

SUBJECT: Open Calendar

As a further step to fulfilling my commitment to an open Agency, I am asking that all FDA officials designated by this memo compile a weekly record showing for the previous week the meetings and events, both open and closed, in which they were involved with regulated industry or other groups and individuals outside the Federal Government. The calendar shall include all meetings, conferences, seminars, speeches, and social events sponsored by regulated industry.

In addition to this retrospective listing of individual meetings and events, each weekly report shall include a prospective listing of all meetings, conferences, advisory committee meetings and other public (open) proceedings of the FDA which do not appear in the monthly FEDERAL REGISTER notice of meetings. Each prospective report shall cover a four-week period.

All reports, both retrospective and prospective, shall be delivered no later than 10:30 a.m., each Friday, to the Office of the Assistant Commissioner for Public Affairs, Room 15B42, Parklawn. ACPA will collate and reproduce the accumulated information and distribute the open calendar by close of business the same day. All reports to ACPA shall be clean typed and suitable for reproduction following the attached format.

Each issue of the open calendar shall be posted in the following places:

1. Public Records and Documents Center, ACC

2. Office of the Assistant Commissioner for Public Affairs (Parklawn and FOB #8)

3. A central place in each Bureau

4. A central place in each Field office

It shall be the responsibility of ACPA to provide copies for posting and it shall be the responsibility of the offices named to select an appropriate place and insure immediate posting.

To avoid duplicate reporting when more than one senior FDA official attends a reportable meeting or event, it shall be the responsibility of the presiding FDA official, or lead participant, to report the meeting or event for the open calendar. No other FDA officials need report. In all such cases, it shall be the further responsibility of the reporting FDA official to prepare a summary memorandum of the meeting or event and to be prepared to respond to public inquiries. Copies of such summary memoranda shall be publicly available on request.

In addition, all officials designated by this memo shall keep a daily log of all telephone calls to and from persons outside the Federal Government. At a minimum, the log shall specify the date, person(s) involved, and the subject(s) discussed. The log shall be publicly available on request.

Detailed requirements for keeping of memoranda on important telephone calls and meetings with non-government sources will be covered under Section 2.11 (g) of the pending procedural regulations. Interim instructions are covered in my memo to all FDA employees dated September 18, 1974.

Meetings and telephone conversations, disclosures of which would compromise regulatory enforcement activities or constitute an invasion of privacy, are excluded from the procedures outlined in this memo. Contacts with members of the working press are excluded.

I realize this system will pose an additional burden on all of us, but I feel it is essential in today's critical climate if the FDA is to maintain full creditability with its own staff and the public. Please understand, therefore, the importance that I attach to compliance with this procedure.

I am fully aware that important outside meetings are held by FDA officials other than those designated for the open calendar. Nevertheless, practicality demands a cut-off at some point, and I feel the point I have chosen will protect the integrity of those levels of FDA leadership responsible for and involved in final decisions on any given matter of policy.

I would emphasize that this formal calendar in no way relieves those FDA officials not designated for listing on the calendar from full responsibility for following all established rules of public accountability for their activities.

Alexander M. Schmidt, M.D.

Attachment

Addressees:
Deputy Commissioner
Associate and Assistant Commissioners
Deputy Associate and Deputy Assistant Commissioners
General Counsel, Deputy General Counsel
Executive Director of Regional Operations, Deputy EDRO
Bureau Directors, Deputy Bureau Directors
Director, Natl. Ctr. for Tox. Res., Deputy Director, NCTR
Director, Office of Legislative Services, Deputy Director, OLS

Format to be Used in Reporting
Calendar Information to ACPA

I. Retrospective Calendar (Public and Closed Meetings)

	FDA OFFICIAL REPORTING*	OTHER FDA PARTICIPANTS	NON-FDA PARTICIPANTS OR SPONSORS	SUBJECT AND MEETING SITE
DATE /	Fill in Name & Title	Fill in Name & Title	Fill in Name, Title & Affiliation	Follow instructions given in footnot (1) & (2)

(1) Subject - Describe major topic discussed in 10 words or less. Examples:

Aflatoxin in Peanuts
Drug Lag
Status of Cyclamate
Pet Food

If discussion is confined to privileged matters, use the following standard phrase: "Meeting involved trade secrets or litigation. Minutes are not available".

(2) Site - Give general identification only. Exclude mailing address. Examples:

FDA-Rockville
FDA-Washington
National Press Club, Washington
American Medical Association, Chicago, Ill.
Hoffman-LaRoche, Nutley, N. J.

II. Prospective Calendar (Public Meetings Not Previously Announced. Do not include Advisory Committee and Other Meetings Which are Routinely Announced in the Federal Register.)

	FDA OFFICIAL REPORTING	MEETING OR EVENT AND SUBJECT	DATE, TIME, PLACE
DATE			

*Minutes of meeting available on request from this office.

SAMPLE SAMPLE SAMPLE

CALENDAR FOR WEEK OF SEPTEMBER 9, 1974

PUBLIC CALENDAR OF OUTSIDE MEETINGS AND EVENTS

FDA OFFICIAL REPORTING*	OTHER FDA PARTICIPANTS	NON-FDA PARTICIPANTS OR SPONSORS	SUBJECT AND MEETING SITE
Sept. 9, 1974			
Sherwin Gardner, Deputy Commissioner	Gerald Meyer, Associate Commissioner	Dr. Randall M. Whaley, President, University City Science Center	Facility Plan FDA-Parklawn
Dr. Fred J. Kingma, Deputy Director, Bureau of Veterinary Medicine		Fred W. Swartz, Government Liaison, Allied Chemical Corp.	Arsenic as growth promot FDA-Parklawn
Dr. Virgil O. Wodicka, Director, Bureau of Foods		6th International Congress of Essential Oils	Speech on "Regulatory Problems with Flavors", Fairmont Hotel San Francisco
Peter B. Hutt, Assistant General Counsel, Food and Drug Division		Christopher Little, Covington & Burling	Interpretation of mastitis or

PUBLIC MEETINGS OR EVENTS NOT PREVIOUSLY ANNOUNCED

FDA OFFICIAL REPORTING	MEETING OR EVENT AND SUBJECT	DATE, TIME PLACE
Oct. 1, 1974		
John Jennings, Associate Commissioner for Medical Affairs	FDA OB-GYN Committee to discuss Dalkon Shield	Oct. 1, 10:00 a.m. Conference Room C FDA-Parklawn

*Minutes of meeting available on request from this office.

SAMPLE SAMPLE SAMPLE

Senator KENNEDY. When are you going to publish your Freedom of Information regulations? You have had them under study now for a year.

Dr. SCHMIDT. This is a massive codification, a revision of the entire procedures of the agency. Your comment would connote a year is far too long for that, but that job is worthy of a long time.

It took a series of meetings of the Agency Policy Board that we run, for 4 or 5 hours over a period of many weeks to resolve the issues, to get them into correct language and to get them written down.

Part of those relating to hearings, that relate to how the agency communicates with and relates to the outside, have already been published.

Part of them are now ready to be published for comment, and then later finalized. Part of them have already appeared.

Senator KENNEDY. Can you give us some idea when they will be published?

Dr. SCHMIDT. Well ——

Senator KENNEDY. Or implemented.

Dr. SCHMIDT. Our general counsel is on vacation the month of August.

Senator KENNEDY. You can submit that.

Dr. SCHMIDT. They should appear by the end of calendar 1974.

Senator KENNEDY. You will give us that as soon as he gets back.

Dr. SCHMIDT. Specifically the freedom of information regulations are ready for publication, but more importantly, we are operating under them now.

Senator KENNEDY. But they have not actually been published, have they?

Dr. SCHMIDT. No, sir.

Mr. VODRA. Well, may I ——

Senator KENNEDY. You might be following them now, but they are not legal binding until they are published. I am just trying to find out when they will be published.

Dr. SCHMIDT. We purposely held up publication of final order until we got the result of a court case that impacted directly on what we wanted to do. We waited for that decision which is now with us. And the freedom of information regulations will be out within weeks.

Senator KENNEDY. They will be finalized when your counsel gets back.

Dr. SCHMIDT. Yes.

[The following information was subsequently supplied for the record:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
ROCKVILLE, MD. 20852

OFFICE OF THE
GENERAL COUNSEL

September 23, 1974

Honorable Edward M. Kennedy
Chairman, Subcommittee on Health
and Subcommittee on Administrative
Practice and Procedure of the
Committee on Labor and Public Welfare
United States Senate
Washington, D. C. 20510

Dear Senator Kennedy:

During the hearing conducted by you on August 16, 1974, relating to Food and Drug Administration procedures in relation to the handling of new drugs, you requested the Commissioner for information relating to the proposed public information regulations published in the Federal Register of May 5, 1972 (37 Fed. Reg. 9128), and the status of the current project to codify in the Federal Register all of the procedures governing the Agency's activities.

With respect to the proposed regulations on public information, issued to implement the Freedom of Information Act, the substance of that proposal has been implemented since May 1972. Final regulations were not immediately promulgated, after the time for public comment expired, for three interrelated reasons.

First, we wished to gain experience under the proposal in order to determine how the final regulations might best be clarified in order to cover all categories of documents contained in the Agency's files which might be requested by the public. We intend to incorporate in the preamble to the final regulations, or in the final regulations themselves, a comprehensive consideration of the status of all these different types of documents in order to provide accurate guidance to the public and to Agency employees. The present draft of the preamble to the final regulations runs in excess of 100 pages.

In this connection, I wish to bring to your attention the fact that, to our knowledge, no government agency has yet attempted to specify by regulation the status of each type of document in its files, in the manner that these regulations do. For the most part, regulations under the Freedom of Information Act have only

repeated the statutory language, or summarized it, without specifying how it will be applied to all of the different types of documents contained in the agency's files. We firmly believe that this type of specific guidance is extremely important, and that the additional time that it has taken to obtain experience under the proposal has been worthwhile.

Second, we also delayed publication of the final regulations to await the outcome of a court suit that we fully expected to adjudicate some of the most important legal issues raised by those regulations. In Morgan v. Food and Drug Administration (D.C. Cir. Civ. No. 71-1709, decided May 24, 1974), the plaintiff sought access to all of the safety and effectiveness data contained in the new drug applications (NDA's) for the oral contraceptive drugs. In the District Court, the Food and Drug Administration took the position that all information in an NDA is confidential and is prohibited from disclosure pursuant to 21 U.S.C. 331(j) and 18 U.S.C. 1905 (both of which make it a criminal offense for an FDA employee to disclose any of this information to the public). The District Court sustained this position in July 1971.

Shortly after the District Court decision, the Food and Drug Administration thoroughly reconsidered its public information program under the Freedom of Information Act, and concluded that it should be substantially modified. We requested that the appeal from that District Court decision be held in abeyance pending publication of proposed new regulations which, as I have mentioned above, were published in the Federal Register of May 5, 1972. We then filed a brief in the United States Court of Appeals for the District of Columbia Circuit which abandoned the position taken in the District Court, and rested upon the much broader scope of release set out in the proposed new regulations. In addition to the brief filed by the plaintiffs and by the government, two briefs were filed for amicus curiae, one arguing that all documents in an NDA are available for public disclosure, and one arguing that, as the District Court held, no such documents may properly be released. Thus, all possible positions were fully presented to the court.

The United States Court of Appeals heard argument in that case on January 22, 1973, and we expected a definitive decision shortly thereafter. The decision of the Court was not handed down, however, until May 24, 1974. Moreover, it was decided solely on narrow procedural grounds, and explicitly declined to reach the broad issues presented by the briefs and the proposed new regulations. A copy of that opinion is enclosed. Accordingly, the expectation of all of the

parties that this area of the law would be settled definitively by this case has not been realized.

Third, we have not been concerned about the delay in publication of the final regulations because we announced at the time of publication of the proposal that the proposal would be implemented by the Food and Drug Administration on an interim basis until final regulations were promulgated.

During the August 16 hearing, you expressed concern that the proposed regulations have no legal effect. I wish to assure you, however, that this is not the situation. We have in fact implemented these regulations, and intend to do so until final regulations are promulgated.

In mid-1972, the Pharmaceutical Manufacturers Association, in correspondence with me and with the Secretary of Health, Education, and Welfare, objected to the immediate implementation of various regulations that were then published only in proposed form, including the public information regulations. I initially provided my opinion that there was no impediment whatever to enforcement of proposed regulations that merely implement statutory requirements, and this was subsequently confirmed in a letter from the General Counsel of the Department of Health, Education, and Welfare to the PMA. A copy of that correspondence is enclosed. As it points out, the right of the public to information is defined by the Freedom of Information Act itself, and is not dependent upon the existence either of proposed or of final regulations.

Subsequent to the decision in the Morgan case, the Food and Drug Administration's Policy Board has met to review and refine its policy on a number of issues raised by comments to the proposed regulations, and I have also met with Bureau personnel to work on a number of specific details. I can assure you that we are proceeding as quickly as possible to publish final regulations. The Commissioner and I have previously stated that the final regulations will clarify and refine the proposal, but that the basic thrust of the proposal — to release substantially more information than was true before 1972 — will not be changed. Most of the changes, indeed, relate to still further release of information. I am not aware that any change will restrict release of information that would be released under the proposal.

Your second area of inquiry during the August 16 hearing related to the project to codify all Food and Drug Administration procedures

in the Federal Register. This is, as I am sure you appreciate, a mammoth undertaking. In reviewing comparable regulations for other agencies, I have not yet found any other government agency which has made a similar attempt.

The first draft of this set of regulations was 177 pages. It has since been substantially revised and lengthened. An explanatory preamble of the type we require for all of our Federal Register notices has not yet been prepared, nor have all of the various provisions been drafted in final form. Indeed, one or two sections remain yet to be drafted in initial form.

The major policy issues have, in large part, been agreed upon by the Food and Drug Administration's Policy Board. The major effort from here on will be to complete the drafting job.

As I have mentioned, these regulations will attempt to establish general and particular procedures for all of the Agency's activities. We have considered the possibility of breaking them apart, and publishing different sections at different times, but we believe this would be confusing because all of the parts are closely interrelated, and drafting changes in one section have frequently required conforming changes in another. We are committed to publishing these regulations in the Federal Register this Fall.

The subjects that will be handled in the procedural regulations will include the following: how all Agency administrative proceedings are initiated; the right of all citizens to petition the Agency; administrative reconsideration of Agency action; administrative stay of Agency action; court review of final Agency action; Agency handling of proposed and final regulations; referral of matters to the Agency by the courts; the handling of conferences, meetings, discussions, and correspondence; dissemination of proposed regulations; advisory opinions; separation of functions and ex parte communications; procedures for formal evidentiary hearings; procedures for informal public hearings and other mechanisms to resolve disputes; procedures governing all advisory committee activities; and a number of related matters. We would, of course, be pleased to keep you and your staff advised of the progress we are making on this major project.

Sincerely yours,

Peter Barton Hutt

Peter Barton Hutt
Assistant General Counsel
Food and Drug Division

Enclosures

United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 71-1709

September Term, 19 73
Civil Action 1928-70

Carolyn D. M. Morgan, Appellant

v.

Food and Drug Administration,
Roger O. Egeberg,
Assistant for Health and Scientific
Affairs, et al

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

Before: McGowan, Circuit Judge, Edwards,* Circuit Judge for the Sixth Circuit, and Wilkey, Circuit Judge

JUDGMENT

This cause came on to be heard on the record on appeal from the United States District Court for the District of Columbia and was argued by counsel. On consideration of the foregoing, it is

ORDERED AND ADJUDGED by this Court that the judgment of the District Court appealed from in this cause is hereby affirmed, for the reasons set forth in the attached memorandum.

Per Curiam
For the Court

Hugh E. Kline
Clerk

*Sitting by designation pursuant to 28 U.S.C. § 291(a)

No. 71-1709 - Morgan v. Food and Drug Administration

MEMORANDUM

Appellant sought access under the Freedom of Information Act to the reports underlying a determination by the Food and Drug Administration that certain oral contraceptives are safe and effective within the meaning of the statutory requirements for the continuing approval of a new drug application. On April 20, 1970 she wrote the Associate Director of Information for Public Services of HEW, asking for permission to examine and make notes of "all materials relating to toxicological tests, safety evaluations, and any other tests, in animals and all reports and records of clinical tests, or any other tests, of such birth control pills in humans." The Associate Director denied appellant's request on May 4 in a letter drawing her attention to the Department's regulations prohibiting disclosure of "[t]rade secrets and commercial or financial information obtained from any person and privileged or confidential." 1/ Appellant sought review of this decision

1/ 45 C.F.R. § 5.74. The quoted language tracks almost precisely that of exemption 4 of FOIA, 5 U.S.C. § 522(b)(4).

by the Assistant Secretary for Health and Scientific Affairs on May 29. When no answer had been received, on June 29, 1970, she filed a complaint in the District Court seeking disclosure. 2/

No action was taken in the District Court until March 23, 1971, when appellant moved for a preliminary injunction to require FDA to grant her access to the test information. On April 8, FDA filed a motion for summary judgment, accompanied by the affidavit of Dr. Henry E. Simmons, the Director of FDA's Bureau of Drugs, and submitted a consolidated memorandum in support of its motion for summary judgment and in opposition to appellant's motion for a preliminary injunction. A hearing on the latter motion was held on April 12, and the motion was denied.

During April and May appellant sought discovery, over FDA's objection, of certain material in its possession. The

2/ On August 10, 1970, before answering in the District Court, the Assistant Secretary affirmed the administrative denial of May 4. His decision was grounded on several of the exemptions of FOIA, including exemption 4.

District Court called a "prehearing conference" for June 16, in order to "narrow the issues and find out where we are at this particular point in the case." Counsel for appellant attended the June 16 conference, and there urged the court to adopt the procedures of the manual for complex and multi-district litigation "with a pretrial order that would list the issues in the case and a schedule that the attorneys would have to abide by plus one wave of discovery ... ."

However, when the court suggested the possibility of an immediate ruling on the merits without further proceedings, appellant's counsel, despite the fact that no opposition had as yet been filed by appellant to the Government's pending motion for summary judgment nor any claim made that there were material issues of fact in dispute (see Rule 56(e) Fed. R. Civ. P., and Local Rule 9), inexplicably agreed. The court a few days thereafter granted the unopposed motion for summary judgment on the grounds that the research test reports were exempt from disclosure both as matter specifically exempt from disclosure by statute (exemption 3) and as either

trade secrets or confidential commercial or financial information (exemption 4).

On this appeal from the grant of summary judgment, the Government relies solely on exemption 4. In the affidavit of Dr. Simmons supporting the motion for summary judgment, there are facts stated that, if taken to be true, would justify the applicability of exemption 4. We have no alternative but to take such facts to be true, inasmuch as appellant was prepared to have the merits of the case determined on appellee's motion for summary judgment without filing any opposition to that motion or asserting that the facts contained in the affidavit were in dispute. Under these circumstances, we cannot say that the District Court erred in granting summary judgment, and affirmance by us is the only course consistent with the procedural posture in which the matter was, with appellant's consent, decided by the District Court. See Thompson v. Evening Star Newspaper Co. 394 F.2d 744 (D.C. Cir. 1968), cert. denied, 393 U.S. 884 (1968).

In reaching this result we are not to be understood as having made any independent determination or intimated any

opinion that the facts asserted in the Simmons affidavit are beyond dispute. All that we decide is that where appellant was prepared to have the merits of her claim resolved without challenging such facts, we are without warrant to reverse the District Court's order.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20201

OFFICE OF THE
GENERAL COUNSEL

OCT 3 1972

Mr. C. Joseph Stetler
President
Pharmaceutical Manufacturers
Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

Dear Mr. Stetler:

As Secretary Richardson advised you in his letter of August 17, 1972, he asked me to review the position taken by the Food and Drug Administration on the various matters relating to implementation of the drug effectiveness review and the Freedom of Information Act about which you had expressed concern in your letter of August 7.

You first suggested that the Food and Drug Administration should consider itself bound to follow on a nationwide basis the legal principle announced on May 23, 1972, in an opinion by the United States Court of Appeals for the Fourth Circuit. As Mr. Hutt wrote to you in July in response to your earlier letters, this Department has been considering whether to seek review of this case by the Supreme Court. In the meantime, believing that the Court of Appeals decision was erroneous and there being no other controlling opinions from the other Courts of Appeals, the Food and Drug Administration is properly, in my judgment, following what we perceive to be the correct rule of law until the issue is finally disposed of in the courts. The acceptance of each lower or intermediate court ruling as defining a new national standard, before the Supreme Court or other courts have spoken and while there is the possibility of further court review, would only lead to instability and confusion in the administration of the enforcement program. Indeed, I understand that it is common practice, not only with Government

agencies, but also in the pharmaceutical industry to withhold changing an already established general practice or rule in the face of a single court decision, applicable only to the immediate litigants, until it is clear that the ruling should be accepted as a definitive ruling on the point in issue.

You next urged that the Food and Drug Administration has been prematurely enforcing two proposed regulations which the Administration has published for public comment but has not yet issued in final form. These regulations relate to the applicability of DESI notices to related or similar drugs, and the implementation of the requirements of the Freedom of Information Act. If you mean to suggest that FDA is presently giving these regulations the force and effect of law (which they would have upon their final promulgation), you are mistaken.

It is our view that FDA has authority under the Food, Drug and Cosmetic Act to apply DESI notices to related or similar drugs without basing that authority on a specific regulation. Indeed, for several years this application of DESI notices has been announced by FDA officials in specific notices in the Federal Register. (See, e.g., 33 F.R. 9908 (July 10, 1968) and 34 F.R. 5556 (March 22, 1969)). The sole purpose of the present Federal Register publication on the applicability of DESI notices is to give more general publication to the practice and to codify it in the Code of Federal Regulations. In the course of this process, FDA is inviting public comment which may, of course, result in modification of its long standing enforcement practice or some different articulation of it in rulemaking form. It would, however, serve no purpose--other than to confuse--for the Administration to discontinue its already established practice or for us to abandon our present view of the Administration's statutory authority, pending the period for public comment.

Similarly, with respect to the Freedom of Information Act proposal, the Food and Drug Administration is simply

putting into regulation form (together with some appropriate implementing procedures) what we conceive to be its responsibility under the Freedom of Information Act to disclose certain records to members of the public on request. While publication of a regulation will give broader notice and more specificity to what we believe is the Administration's obligation under the Act, the pendency of the period for public comment upon the proposed regulation cannot excuse us from performing our duty under the Act. The right of the public to information is defined by the Act and is not dependent upon the existence of regulation.

Your more specific complaint regarding disclosure of records is that certain disclosures called for by the terms of the proposed regulation are contrary to assurances of confidentiality given to the pharmaceutical industry by the Food and Drug Administration. The proposed regulation itself, however, will provide a procedure by which any aggrieved pharmaceutical firm may challenge the Administration's determination that a particular record should be disclosed. Insofar as disclosures during the period for public comment on the proposed regulation are concerned, Mr. Hutt informs me that disclosures which would be subject to this procedural safeguard are now being made only after discussion with the company or individual who submitted the information. So far, with only one unfortunate exception which was contrary to the Administration's present practice, no information of this sort has been disclosed where the company or individual objected. In the event of objection, actual disclosure will be withheld for 10 days to allow time for the objecting company or individual to seek court review.

Should you wish to pursue these matters further, Mr. Hutt and I would be happy to meet with you at your convenience.

Sincerely,

Wilmot R. Hastings
General Counsel

cc: Dr. Edwards
Mr. Hutt

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D. C. 20201

C
O
P
Y

August 17, 1972

Mr. C. Joseph Stetler
President
Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

Dear Mr. Stetler:

Thank you for your letter of August 7 concerning recent activities of the Assistant General Counsel, Food, Drugs, and Product Safety Division. I note you have furnished copies of your letter to Charles C. Edwards, M.D., and Peter Barton Hutt, Esquire.

Mr. Hutt, in whom I have complete confidence, is on a well deserved vacation from which he will return in early September. Any comment on what you consider to be problems due to Mr. Hutt's activities will necessarily be delayed until after Mr. Hutt returns to his office, has an opportunity to review your letter, and to furnish his views on the points you raise. I have asked our General Counsel, Wilmot R. Hastings, to pursue this matter with Mr. Hutt.

With kindest regards,

Sincerely,

/s/Elliot L. Richardson

Secretary

PHARMACEUTICAL MANUFACTURERS
Association
1155 FIFTEENTH STREET, N.W.
WASHINGTON, D.C. 20005
AREA CODE 202-296-2440

C. JOSEPH STETLER
PRESIDENT

August 7, 1972

The Honorable Elliot L. Richardson
Secretary
Department of Health, Education,
and Welfare
Washington, D.C. 20201

Dear Secretary Richardson:

It has long been the policy of the Pharmaceutical Manufacturers Association and its member companies to cooperate with the Food and Drug Administration whenever possible in order to promote effective and fair regulation for the benefit of the public. There are times, however, when serious differences of opinion as to the requirements of law and regulation arise. In such circumstances, neither the agency nor the Association have hesitated to seek redress from the courts. It has always been our assumption, however, that neither party would knowingly disregard the law once an issue has been adjudicated. Some recent activities of the Assistant General Counsel, Food, Drugs, and Product Safety Division, have cast serious doubts on this assumption. Specifically, he has stated that he does not intend to comply with a recent decision of the U.S. Court of Appeals for the Fourth Circuit (Bentex v. Richardson et al (No. 71-1234, May 23, 1972)). That case held that manufacturers of drugs never covered by NDAs could not be made subject to decisions on similar drugs covered by new drug applications. The Assistant General Counsel, in a letter to PMA's Vice President and General Counsel dated July 25, wrote, "With respect to the Court of Appeals decision, it would be irresponsible for us to comply with an incorrect statement of the law". It is one thing for a government agency to appeal a decision or to seek a different ruling in other jurisdictions, and quite another to arrogate to oneself the decision of whether to obey the law.

We are also concerned by another development which we consider to be violative of the Administrative Procedure Act. Involved are two agency regulations which have been published in proposed form which are being enforced by the Food and Drug Administration as if they were final orders. These actions are being taken on the instructions of, or at least with the knowledge of, the Assistant General Counsel.

One proposal dealt with the scope of the applicability of notices implementing the NAS/NRC panel findings to drugs subject to new drug applications. In essence, the order would apply such findings to related or similar drugs to those mentioned in the notice even though such drugs were not themselves subject to new drug applications. In a letter dated July 3, 1972, the Assistant General Counsel stated that he was already applying the order to such drugs and, indeed, had been for some time. (Enclosed are copies of correspondence relating to the problems described above.)

The second regulation consists of a comprehensive set of rules purporting to implement the requirements of the Freedom of Information Act to the volumes of files maintained by the Food and Drug Administration (37 FR 9128 ff of May 5, 1972). Under the order, much of the material previously held in confidence by the FDA would now be subject to disclosure. Much of this data had been received by FDA pursuant to agency-industry understanding that they would be maintained as confidential.

The Assistant General Counsel has advised the PMA that the proposal is now being implemented and enforced. Further, we have been informed by some of our member companies that officials in the Bureau of Drugs of the FDA have been told that the proposed order should presently be enforced.

The premature enforcement of these regulations clearly violates the basic requirements of the Administrative Procedure Act. Of what value is a statutory mandate to permit interested parties to comment on a proposed regulation before finalization or to challenge the final order in court if the order "under consideration" is implemented even prior to the time comments are received? With regard to the determination to release information in FDA files, we must strenuously object to the unilateral decision to release information previously received under a promise of confidence. In addition to being a violation of the Freedom of Information Act, such action constitutes a conscious and deliberate breach of faith with the regulated industry.

I regret that it has become necessary to inform you of these actions. However, I am sure that you can appreciate their seriousness to ours and the other industries involved. I would appreciate your comment on the problems raised in this letter.

Sincerely yours,

C. Joseph Stetler

C. Joseph Stetler

cc: Charles C. Edwards, M.D.
Peter Barton Hutt, Esq.

Enclosures

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20201

OFFICE OF THE GENERAL COUNSEL

July 25, 1972

Mr. Bruce J. Brennan
Vice President and General Counsel
Pharmaceutical Manufacturers
Association
1155 - 15th Street, N. W.
Washington, D. C. 20005

Dear Mr. Brennan:

This is in response to your letter of July 21, 1972, relating to FDA's policy on the application of DESI notices to related drugs. Our policy on this matter has been known for several years. It has been enunciated in numerous DESI notices, talks, and letters by FDA officials. It hardly comes as a surprise to industry and the public. The proposed regulation merely brought it together in one place.

With respect to the Court of Appeals' decision, it would be irresponsible for us to comply with an incorrect statement of the law. We have requested the Solicitor General to seek certiorari in the cases involved.

We remain of the opinion that DESI notices constitute a determination that non-complying products are misbranded, and that the grandfather clauses of the law do not protect non-complying products from misbranding charges. As you point out, a determination of misbranding means only that the product may not be legally marketed in that form. Any subsequent marketing in a revised form, with labeling that does not constitute misbranding, would in our opinion inherently make the grandfather clause inapplicable.

I appreciate having your views on this matter.

Sincerely yours,

Peter Barton Hutt

Peter Barton Hutt
Assistant General Counsel
Food, Drugs, and Product
Safety Division

July 21, 1972

Peter Barton Hutt, Esq.
Assistant General Counsel
Food, Drugs, and Environmental
Health Division
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Hutt:

Thank you for your letter of July 3 responding to my June 20 inquiry questioning FDA's policy on the application of DESI notices to related drugs.

We do not believe it to be a proper practice to implement a policy and then publish a proposed order suggesting that policy and requesting comments. Such a procedure ignores the requirements of the Administrative Procedure Act. Further, we believe that Agency disregard of a decision by a U.S. Court of Appeals is not responsible action on the part of Government.

I note that you state in your letter that "DESI notices constitute a determination that noncomplying products are misbranded and that the grandfather clauses of the law do not apply to misbranding". While we recognize that the FDA may view any product as misbranded, no such view can have any legal effect until upheld by a U.S. Court, based upon appropriate proof in a civil or criminal case. In addition, even a determination of misbranding does not result in the inapplicability of the grandfather clause to the subject drug, unless and until its labeling is substantially changed.

While action at this time by PMA has not been determined, I believe it important that you have our views on these matters.

Sincerely,

Bruce J. Brennan

PHARMACEUTICAL MANUFACTURERS
Association
1155 FIFTEENTH STREET, N. W.
WASHINGTON, D. C. 20005
AREA CODE 202-296-2440

July 7, 1972

TO THE REPRESENTATIVES ON THE LAW SECTION

As a result of the decision in Bentex, et al v. Richardson, et al (No. 71-1243, May 23, 1972), the enclosed correspondence was initiated. The first portion of the response from FDA General Counsel Hutt needs no amplification. However, please take note of the final paragraph of Mr. Hutt's letter. The assertion that "DESI notices constitute a determination that non-complying products are misbranded" has not been officially pronounced by FDA prior to this time to our knowledge.

BRUCE J. BRENNAN
Vice President and
General Counsel

Enclosures

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Office of the Secretary
Rockville, Maryland 20852
July 3, 1972

Mr. Bruce J. Brennan
Vice President and General Counsel
Pharmaceutical Manufacturers Association
1155 - 15th Street, N.W.
Washington, D. C. 20005

Dear Mr. Brennan:

This is in response to your letter of June 20, 1972, in which you request that appropriate FDA officials be notified that related drugs are not covered by DESI notices.

For some time before the proposal published in the Federal Register for February 10, 1972, FDA has been applying DESI notices to related drugs. That proposal is intended simply to inform the industry of this enforcement practice. Accordingly, publication of that proposal provides no reason for temporary discontinuance of this type of enforcement.

The Bentex decision, to which you refer, is in our opinion not a proper interpretation of the new drug provisions of the law. We are taking the steps necessary to obtain further judicial review of that decision and/or further judicial clarification of this aspect of the law in other jurisdictions. Accordingly, we will not discontinue enforcement of DESI notices against related drugs on new drug grounds on the basis of that decision.

Finally, the DESI notices constitute a determination that noncomplying products are misbranded, as well as illegal new drugs. As you know, the grandfather clauses of the law do not apply to misbranding. We will therefore also continue to enforce DESI notices against related drugs on misbranding grounds.

Sincerely yours,

/s/

Peter Barton Hutt
Assistant General Counsel
Food, Drugs, and Product
Safety Division

COPY

Association
1155 FIFTEENTH STREET, N. W.
WASHINGTON, D. C. 20005
AREA CODE 202-296-2440

June 20, 1972

Peter Barton Hutt, Esq.
Assistant General Counsel
Food, Drugs, and Environmental
Health Division
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Hutt:

Recently, some of our member companies have brought to our attention that FDA is attempting to enforce 37 FR 2970 of February 10, 1972, even though the proposal has not yet been published in final form. The proposed order referred to is entitled in part "Applicability of DESI Notices to Identical, Related and Similar Drug Products". Apparently, the attempts to implement the proposal, in addition to being premature, do not take into account Section 107(c)(4) of the Drug Amendments of 1962 which exempts certain so-called "me-too" drugs from application of the "effectiveness" portion of the new drug definition. You will recall that the United States Court of Appeals for the Fourth Circuit in Bentex, et al v. Richardson, et al (No. 71-1243, May 23, 1972) held that manufacturers of drugs never covered by NDAs which were "grandfathered" on October 9, 1962, would not be made subject to new drug application requirements in most circumstances.

We urge that the appropriate FDA officials be notified that the related drug proposal has not been finalized and of the ruling of the Bentex case.

I would appreciate your early reply in this matter.

Sincerely,

/s/

Bruce J. Brennan

Senator KENNEDY. Could you tell us a little bit about your policy of transferring people?

Dr. SCHMIDT. Yes. Because I have told the Bureau of Drugs what my policy is, and I would say what mine is, Dr. Crout may amplify because his policies are important,

In general, I believe that people should be doing a job in which they are effective and efficient and happy.

Senator KENNEDY. What about qualifications?

Dr. SCHMIDT. If three people—sir?

Senator KENNEDY. Does qualification matter?

Dr. SCHMIDT. Well, I believe that is implied by my use of the word "effectiveness."

Senator KENNEDY. I see.

Dr. SCHMIDT. Now, I am not hung up on rigorous qualifications for a job, because I will state to you directly that my criterion is effectiveness. Of getting the job done. And I have sometimes put people who were "unqualified" in a job and they have done fairly well.

Now I will move people who are unable or unwilling to be effective and efficient in their jobs, and I will put the good of the organization before the good of an individual in terms of his happiness. Because it is more important for the organization, in general — and it is an important organization—to be effective than it is for each and every individual to be happy.

Senator KENNEDY. This, again, sounds awfully nice, Mr. Commissioner, but we heard yesterday from 11 witnesses, who disapproved different drugs, and in many instances had their findings upheld by review and advisory committees, and all were transferred out of their areas of expertise, into other areas where I think uniformly they felt their talents, efforts and energies were not being utilized.

Now, that is a pretty compelling pattern.

Dr. SCHMIDT. Well, I can give you now a range of possibilities, and then after my investigation supply a more satisfactory answer.

The range of possibilities for transfers would include agency needs in other areas. I will transfer somebody if there is a priority area someplace else and he is needed there.

The range of possibilities also include incompetence or an unwillingness to do a job when asked. It goes through a spectrum of possible reasons.

Senator KENNEDY. Well, it seems to me that if they are unwilling or incapable of doing a job, you would take action to remove them from the agency.

But we are talking about a different pattern here. I am sure you will give us some explanation. We will welcome it. But they are patterns which I would think, you would be very much concerned with, as they don't seem to relate much to incompetency or unwillingness.

Dr. SCHMIDT. Well, if your assumption—and I assume it is an assumption, not a conclusion—of a pattern is valid, then I would guess there may be a pattern to the reasons, and I would be as interested as you in finding that out.

Senator KENNEDY. Take Dr. Nestor, for example. He did excellent work in MER–29. Mr. Meyer, who is the former Office of Legislative Services, says he believes that Dr. Nestor is now in a position to make a greater contribution to the protection of the public from harmful

products. I think he said Dr. Nestor said he had not done 3 months' work in 2 years.

Dr. SCHMIDT. I saw that and was shocked by that. [Laughter.]

Senator KENNEDY. So were we.

Dr. SCHMIDT. It really makes me wonder about the individual.

Senator KENNEDY. It makes me wonder about the agency.

I think to try to impugn his service is unjustified based upon his record, which I think stands pretty tall. We are not going to let you take any of the witnesses who were here and destroy their effectiveness. "I want to make that perfectly clear," as it were, and I am sure I speak for every member of these committees, Republican as well as Democrat. I certainly hope that in your review you are not going to start off by saying we have a lot of misfits here, boys, let's get the justification on it, because if you could have listened to these people and heard how they care about the agency and the pride they have in their work, and what it means to them in terms of their professional competency to have the distortions that have been made against them, you would have been disturbed. That was an indictment, Mr. Commissioner, and you could not escape it from listening to those witnesses yesterday.

Dr. SCHMIDT. If I may just make a personal note, I am a little disturbed that you make such a point to assure my responsible behavior.

Senator KENNEDY. I am not sure that I caught what you said.

Dr. CROUT. I hope the record will also read that some others of us have laid our professional careers on the line to serve the people through the Food and Drug Administration. I think there is generally the assumption that there are white hats and black hats and somebody is on the carpet. Your study of the agency will more likely find out the truth if it is gentle on the people involved.

We are dealing with a lot of people who have deeply felt motivations, including management. We are dealing also with an admixture of personnel problems, false assertions, true issues, and deep issues of policy. We simply would like to get the chance to straighten them out in a healthy and a warm environment before there is mistaken testimony or impression about the competence of the entire agency.

It would be a disservice to the American public for them to think that an agency we are responsible for is behaving in the manner in which you have gotten the impression. We are very concerned about it.

Senator KENNEDY. Well, I appreciate that. By raising the issues regarding the pattern of harassment, we do not downgrade other people in the agency. What it does probably reflect is a good deal of administrative problems. These stories are so. And in listening to them, I for one felt it was extremely powerful and compelling testimony.

I gathered from what was said this morning that you are going to promulgate rules and regulations. But I dare say that your statements of what is policy at FDA and what is being carried out are not the same.

I also asked you to show us some written information. You do not have that, Mr. Commissioner, or at least we haven't seen it.

Now, we are going around again.

Dr. CROUT. You can hardly expect me to have come with minutes.

Senator KENNEDY. Exactly.

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Dr. CROUT. With memoranda and so on, to document the policy issues that have arisen here.

We will respond completely and as quickly as we can, now that we know what—and when we know specifically what we are investigating.

Senator KENNEDY. All right. Just a final few minutes, Doctor.

Do you believe that the raw data is essential to make an informed judgment on an NDA?

Dr. SCHMIDT. Yes.

Senator KENNEDY. And do advisory committees usually review raw data?

Dr. SCHMIDT. No; they do not usually review raw data.

Senator KENNEDY. Should they?

Dr. SCHMIDT. I think that in certain circumstances that is warranted, yes. But I do not believe it is possible or profitable, nor do the advisory committees themselves either want or need, in all instances, raw data.

It is occasionally extremely voluminous; it is occasionally hard to draw together. Among the things we are doing is changing the way data have come into the agency, changing the way the data presented are organized so that the data can be more generally useful. But it would be an impossible task for the committees to routinely review the raw data.

Senator KENNEDY. This is one of the contributions made yesterday by Dr. Freeman and Dr. Solomons. I am not sure which one, but one of them made the observation that the summary data that was provided to them was misleading and inaccurate, and was not justified in terms of the raw data that they reviewed.

Dr. SCHMIDT. Now, once again——

Senator KENNEDY. I understand that you were understandably not prepared with documentation. But the point is that someone has to review that raw data and it would appear to me that the persons who do review it have the burden of proof, and consequently their recommendations should receive considerable weight.

Can you tell me why, in your procedures, Mr. Commissioner, what review is there made of a favorable decision on an NDA?

Dr. SCHMIDT. The process presently—and I stress presently because, you know, we have admitted that things are changing and have changed—is identical for the drugs that are approved and the drugs that may be disapproved.

There is no difference in the way the two are handled.

Senator KENNEDY. Well, again, Commissioner, there were 11 people yesterday, mostly medical officers, who said that when they approved an NDA, to their knowledge, that decision never was overturned. Their judgment was questioned only when they disapproved it.

Dr. SCHMIDT. In my statement I made one point that is natural and true, and that is that within the process, which is identical, if everyone agrees, there will not be the questioning and the discussion that there will be if there is disagreement. That is factual and logical.

And there used to be differences. Formerly, one individual within the Bureau of Drugs could stop a drug and there were different pathways for approvals and disapprovals, but that is no longer true.

Dr. Crout may be able to amplify.

Dr. CROUT. I think there is a real misconception that should be corrected. In the first place, most new drug applications are eventually approved. A disapproval on a new drug application is uncommonly a permanent turndown of that drug.

If drugs are turned down permanently for lack of safety or efficacy, those problems are generally discovered during the IND process in our system, which is a good way to do business. An NDA is usually not submitted.

So the idea that turning down NDA's is in some way equivalent to protecting the public on a safety issue is not correct. We should be protecting the public on safety issues well before any drug reaches the NDA stage.

Now, if we send out a nonapproval letter, that must list in it the deficiencies, and that letter is subject to legal challenge. It is a demanding exercise to write a good nonapproval letter.

In contrast, if we write an approval letter, the letter itself is quite easy. But the scientific inquiry at that point is directed to what is the evidence supporting safety and efficacy, and is the labeling proper.

Now, I can assure you that these two things are handled equally. Both approvals and nonapprovals are signed off by the Bureau Director. There is a great deal of recycling of applications, both approvables and nonapprovables, more recycling than we would like sometimes, from upper levels of the bureaucracy to lower levels. And the purpose is to build a good record, to see that the documentation is correct. The right decision must be made for the right reason and be documented correctly. I know simply of no basis for any statement that, in the last 2 years at least, drugs which are approved or not approved are handled differently. Both go to advisory committees. Both go to rounds. Both are signed off by the same people. We exercise the same care in the review of data. It is completely a false issue to think that a responsible manager is interested in having his name attached permanently to some future drug disaster.

That is just completely stupid for people to think that persons known to the public—the Commissioner, myself, Dr. Finkel, and so on—want to have another thalidomide weighing on our consciences.

Now, I will say that during the 1960's, the system was that approvals went up to the Commissioner for signature, while nonapprovals could be signed off by either the medical officer first or later by the Division Director.

So at that time, when nonapprovals went out at a lower level of the bureaucracy, there were a large number of appeals to the Commissioner about these nonapprovable letters. From this stemmed, I think, a number of troubles you heard about, of members of management meeting with industry and so on.

Now, that is a bad system. We recognize it as such and have changed it.

But I wish to state very forcefully that approvable letters and nonapprovable letters are handled exactly the same. And I will welcome, I welcome open study by anybody of any deviation from that practice in the last couple of years. Any alleged deviation.

Senator KENNEDY. Can you tell us how many approved recommendations in the last 2 years have been overturned by a review committee?

Dr. CROUT. How many——

Senator KENNEDY. Approved.

Dr. CROUT. Again, I point out that the issue of approvable-nonapprovable seldom goes in that form to an advisory committee.

The questions are usually if it is approvable: What should the warning say? Do we have sufficient data for this indication? Do we include other indications in the labeling.

These are the kinds of questions which come to advisory committees.

Senator KENNEDY. Right. But not whether it should have been approved?

Dr. CROUT. Well, they are then asked, in certain circumstances but not every one, do the data, in your opinion, support the safety and effectiveness of this drug.

Now, it is quite rare for an advisory committee to disagree with the Food and Drug Administration staff on that point, because a correct review by good people, as you pointed out, presented to good consultants, is very likely to lead to the same judgment.

Now, I do not recall a new drug application which has had in the last 2 years a nonconcurrence attached to it on the part of the medical officer or pharmacologist.

There are some where the original reviews recommended nonapproval. But then new data come in or there is a recycling, or something, and there is a re-review. But by the time a new drug is fully approved for marketing, there is generally widespread concurrence among the FDA staff and the consultants or advisory committees on that decision.

There may be some real differences of opinion on what the labeling should say, that sort of thing, but the fundamental issue of approvability is rarely contested.

I sign off on, perhaps, 8 or 10, probably, new applications a month. Not quite that, 5 to 8.

More than half of those, both approvables and nonapprovables, recycle from my office back down again for certain problems, and this recycling includes both the approvables and nonapprovables.

They always go back to the Division. They always go to the review team.

I have never signed a new drug application on which I did not see what I thought was a fully competent medical officer's review, and if there isn't one, it goes back again.

Senator KENNEDY. Well, I thank you, Mr. Commissioner. The variations in the presentations made yesterday and today are really dramatic.

I think this is what this committee is interested in, and we will be looking forward to working with you on it.

I think these charges and allegations are extremely serious.

I for one feel that the Food and Drug Administration itself in terms, of protecting the public interest in drugs, has a record which is unparalleled in any country in the world, and I think all Americans should recognize this. But that does not mean that it cannot be made a great deal better, because the allegations that have been made in the course of those hearings yesterday were extremely shocking and distressing. We need responses, direct and specific. I hope that you are going to take every possible step within the agency to effect remedies for these patterns of harassment.

So we are going to look forward to working with you on this particular issue.

Dr. SCHMIDT. Thank you. I appreciate your last comment, and particularly your comment about the work of the Food and Drug Administration, because I really believe that is important.

None of us sitting here before you would claim that bad things have not at one time or another happened in the administrative practices of the agency; and all of us, as Dr. Crout I think quite eloquently said, are dedicated to getting to the bottom of what I would agree was highly disturbing testimony yesterday; and please know that we will work very hard to improve the agency in any way that the evidence would show that it needs improving.

Senator KENNEDY. I am very happy to hear that. We on this committee, having worked with FDA for years, are in a particularly good position to appreciate the generally outstanding record of the FDA, and we are as anxious as you are to correct those patterns of abuse which detract from that record. We will look forward to working with you to help you do so.

I want to thank you very much.

[The prepared statement of Dr. Schmidt follows:]

STATEMENT

BY

ALEXANDER M. SCHMIDT, M.D.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON LABOR AND PUBLIC WELFARE

UNITED STATES SENATE

AUGUST 16, 1974

Mr. Chairman:

We are pleased to have the opportunity to appear before your Subcommittee to discuss the impact of our regulatory system on the development and marketing of drugs in this country.

Mr. Chairman, I would like to state that we believe the United States' system of drug regulation allows the drugs marketed in this country to be the safest, most effective medicines in the world. Nevertheless, as you well know, serious concerns have been voiced. Some critics allege that we have been too lenient in removing unsafe or ineffective drugs from the market, while still others charge that our system frustrates the development and introduction of new drugs. Some of these concerns are:

-- The 1962 Kefauver-Harris Amendments and their implementation by the Food and Drug Administration have unnecessarily hampered new drug development in the United States, and have driven drug research abroad.

-- There is a growing therapeutic gap between this country and other nations of the world.

-- There is a decline in the number of important new drugs entering the market in this country.

-- That drugs are approved without being safe.

-- That ineffective and dangerous drugs are not removed from the market.

These concerns have not been lightly dismissed by the Food and Drug Administration. On the contrary, we are very interested by them, and have carefully examined them. We have identified several significant issues that relate to these charges and which I would like to discuss. These include:

-- Public policy.

-- Scientific advances since 1962.

-- Differences in drug laws and regulations between nations.

-- Requirements of 1962 Drug Amendments.

-- FDA's implementation of the 1962 Drug Amendments.

To place in perspective my discussion of these factors, it is necessary to first address the question--Has the number of new pharmaceuticals approved in the United States been declining?

THE RATE OF DRUG INTRODUCTION IN THE UNITED STATES

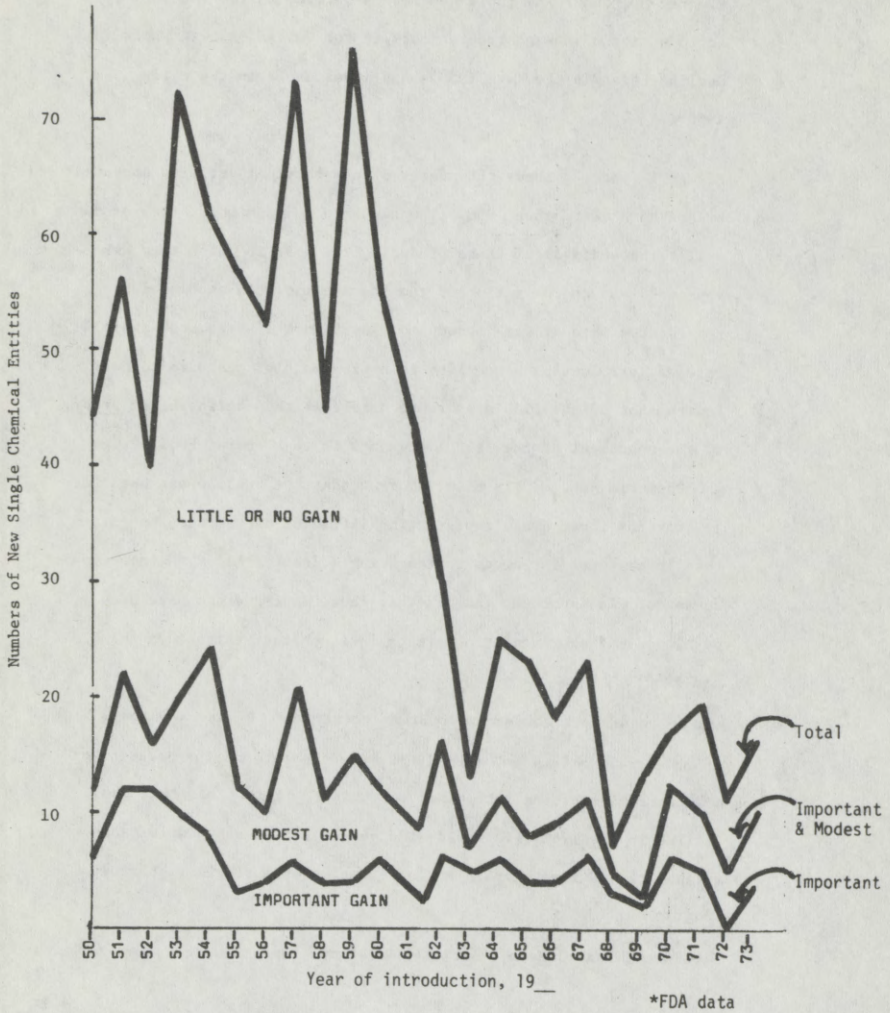
Clearly Mr. Chairman, there has been a decline in the rate of introduction of new pharmaceuticals in the United States. This decline began in the late 1950's and leveled off in the early 1960's.

Figure 1 (page 4) shows the number of new chemical entities approved by FDA each year since 1950. I would like to submit for the record a list (Appendix A) of these products, the year in which they were approved, and an FDA rating of the therapeutic gain each product represented when it was introduced. As figure 1 shows, the overall rate of introduction since 1960 is approximately one-third to one-fourth that of the 1950's. Please note that the decline began prior to the enactment of the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act. It is also apparent that the decline has been far greater for those drugs representing little or no therapeutic gain than it has been for drugs representing modest or major therapeutic advances. An important fact is that these latter drugs have been developed and approved at a more or less constant rate since the mid-1950's.

How do these data compare with other countries? Figure 2 on page 5, using data from Paul deHaen*, illustrates the rate of introduction of new chemical entities into other countries. It is clear that the decline in the 1960's is world-wide and cannot have a simple cause or a cause that exists only in a single nation or a single regulatory program.

*President, Paul deHaen, Inc., 111 W. 42nd Street, New York, New York

FIGURE 1. YEARLY APPROVALS OF NEW DRUGS REPRESENTING VARIOUS DEGREES OF THERAPEUTIC GAIN US, 1950-73*



*FDA data

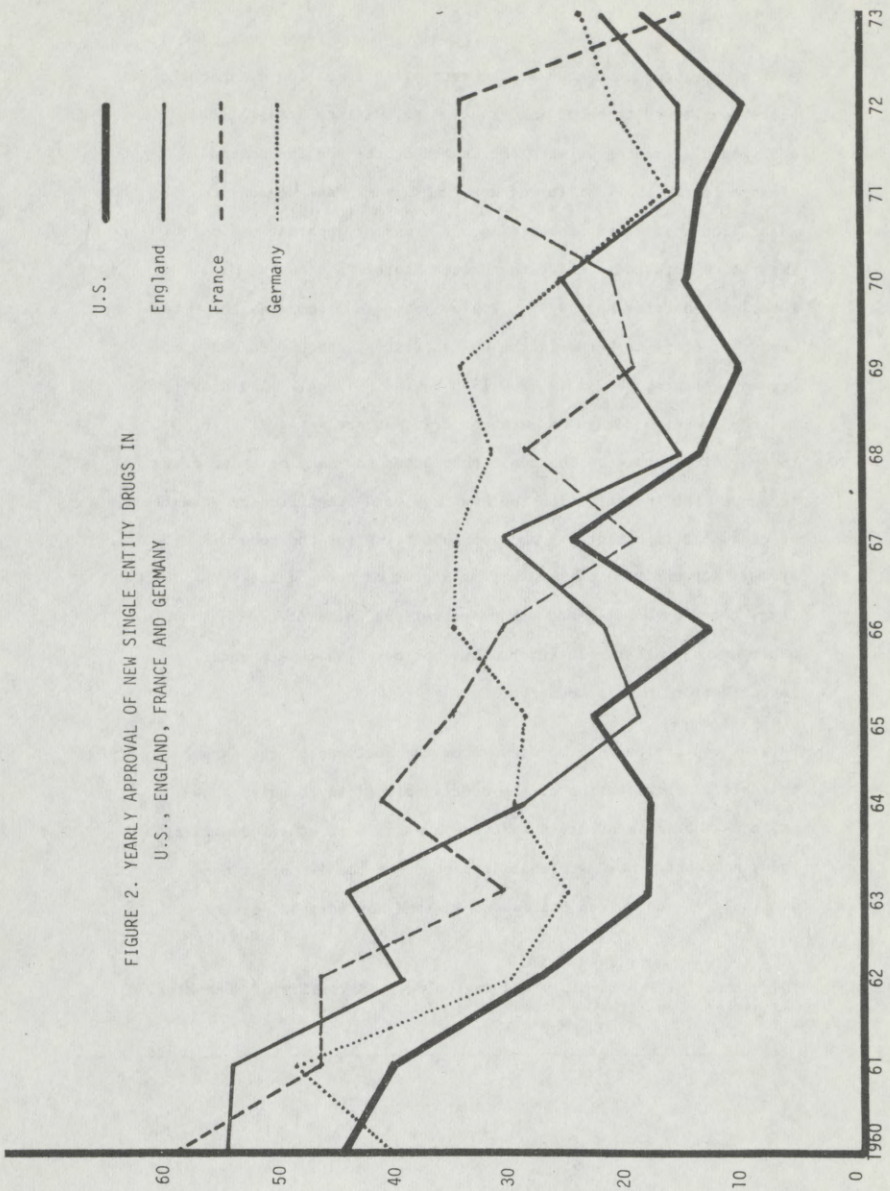


FIGURE 2. YEARLY APPROVAL OF NEW SINGLE ENTITY DRUGS IN U.S., ENGLAND, FRANCE AND GERMANY

Many people have commented on the rate of introduction of specific drugs considered to be of importance. Dr. William Wardell* has analyzed differences between the United States and the United Kingdom in the availability of new drugs. Mr. Paul deHaen has identified a selected number of other drugs of apparent medical importance marketed outside the United States in a number of European countries and Japan. Table 1 on page 7 compares the total number of drugs marketed in the United States, the United Kingdom, Germany, France, and Italy from 1960 to the present. Also shown are the number of drugs in each country that are not available in the United States. The table then notes how many of those drugs are under IND investigation and how many were identified by Wardell or deHaen as important. I am also submitting for the record a summary (Appendix B) of the current status of each of the drugs cited by Wardell and deHaen as well as the status of other drugs available in Europe (but not here) which are under investigation in this country.

Several conclusions can be drawn from the analyses of the data in Table 1. Examination of the drug supply of any country shows it to be lacking many drugs that are available in other countries. Thus, no country has more than 48 percent of the 590 drugs not available in the United States and England has only 32 percent.

*Department of Pharmacology and Toxicology, University of Rochester, Rochester, New York.

Table 1

COUNTRY	NEW DRUGS MARKETED 1960-1973 (1)	DRUGS MARKETED IN COUNTRIES OTHER THAN U.S. NOT YET IN U.S. (2)	DRUGS NOT IN U.S. HAVING AN IND (3)		DRUGS NOT IN U.S. LISTED AS IMPORTANT (4)		DRUGS LISTED AS IMPORTANT HAVING AN IND IN THE U.S. * (5)			
UNITED STATES	295 (307)+	----	----		----		----			
			ACTIVE	INACTIVE	WARDELL	deHaen	WARDELL		deHaen	
							A	I	A	I
ENGLAND	411	186	66	29	93	39	41	25	24	8
FRANCE	467	283	40	30	43	44	20	13	21	12
GERMANY	432	211	57	37	43	54	26	9	24	9
ITALY (1964 - 1973)	(212)	(124)	48	18	32	35	24	5	21	6
JAPAN (1969-1973)	(111)	(79)	18	8	12	23	9	3	9	4
TOTAL IN FIVE FOREIGN COUNTRIES[a]	950	590	124	72	100	110	48	25	48	18
			196		158[b]		73[c]		66[c]	

Source: Basic Data, Paul deHaen, Inc., New York, NY, corrected for approvals and INDs as of July 31, 1974.

+ FDA data

a These totals are not the sum of numbers in the columns 1-5. Many drugs are introduced in more than one country, so that adding the numbers for each country would represent double-counting.

b Cited either by Wardell (W) or deHaen (D); W only, 74; D only, 84; both, 26. *A=Active I=Inactive IND

c Of the 158 drugs cited either by Wardell or deHaen, 114 have INDs; 78 active and 36 inactive.
Of the 26 drugs cited by both, 25 have INDs; 18 active and 7 inactive.

Moreover, of the products not available in this country, the majority duplicate drugs which are already available in the United States. Only 196 are of sufficient interest to manufacturers to have generated an IND, of which only 124 are active. Further, most are not identified by the Wardell or deHaen studies as of potential therapeutic importance. The important issue is not the number of new drugs not marketed in this country, but whether any are of therapeutic importance, given what is already available in the United States.

In February 1973, FDA testified before the Subcommittee on Monopoly that among the drugs not available in the United States, there were no therapeutic breakthroughs or life-saving agents for which an equally effective alternative was not already available in the United States. We have again reviewed this list and reached the same conclusion with one exception. A drug called salmon calcitonin, similar to a drug marketed in Europe, now appears to provide effective treatment for a sometimes debilitating disease of bone called Paget's Disease. Review of the NDA for this drug is nearly complete.

Although the list in Appendix B includes (again with one exception) no "breakthroughs," we would emphasize that it does contain drugs which appear to offer convenience gains, and in some cases an improved benefit-risk ratio compared to drugs available in the United States. We are concerned

that these particular agents are not yet available in the United States and are subjecting this problem to close scrutiny.

A second aspect of this problem, Mr. Chairman, is the shift abroad of drug investigation, especially its early phases. Industry knows better than we do the extent to which this has occurred, but it is clear that we now see more drugs for the first time only after they have been studied in Europe. We are concerned about this trend because it may weaken our own national capacities in clinical investigation in therapeutics and exaggerate the delay in the introduction of useful new drugs here. It will also shift to other countries responsibility for dealing with the ethical and scientific problems raised by modern research in which the United States should properly participate. I would now like to turn to a brief discussion of some of the issues that have contributed to this situation, or may affect it in the future.

PUBLIC CONCERN

An extremely important issue in recent years in influencing the development and marketing of drugs in this country has been the rising concern of the public about drug safety, as well as about the ethical aspects of human research. We live in an era of increasing skepticism about the value of new drugs when compared with the risks of developing and using them. As more drugs are developed; as more therapeutic gaps are filled, people begin to ask hard questions

about the new drugs still under development. Do we really need them? What do we know about their safety in long-term use? How much can we trust that the animal toxicology tests they have passed will really protect us? If a serious toxicity is discovered in animals, will that necessarily occur in man? How much risk should we take finding out the answer to that question?

There is, in addition, increasing concern with the ethics of human drug investigation. Questions have been raised about whether informed voluntary consent can really be obtained from prisoners, minors, or patients in mental hospitals; and about whether institutional review committees as presently constituted provide adequate protection of patients' interests.

It is evident that public concern with drug investigation, like Federal regulation of drug investigation, can make drug development more difficult and more expensive. This clearly can cause such investigation to move abroad, but it also has clear benefits in terms of assuring the public safety. How the potential loss of new therapies due to decreased drug development should be weighed against the potential risks of human investigation is an issue of great complexity. This important judgmental issue must be addressed by representatives of many interests and disciplines and ultimately must be resolved by the public.

Next, let us consider the impact of scientific advances since 1962 on drug development.

SCIENTIFIC ADVANCES

As we all know, there has been an enormous growth in the past two decades in biomedical knowledge, in the sophistication of research, and our ability to develop new information about a drug. An example of which you are well aware, Mr. Chairman, is the relatively new field of bioavailability and another is drug-drug interactions. While many useful entities have been developed and marketed in the past without knowledge of bioavailability and potential drug interactions, we cannot ignore these issues today. Regulatory requirements for more information undoubtedly slow new drug introduction, but such requirements have also stimulated acquisition of important new scientific and medical knowledge about new drugs.

Today's world includes a great number of important therapeutic agents unknown a generation ago. These include antibiotics, antihypertensive drugs, diuretics, antipsychotic drugs, tranquilizers, cancer chemotherapeutic agents, and a host of others. This therapeutic achievement has occurred because of the applied research efforts of the drug industry in a society which also values and supports fundamental research aimed at the expansion of biomedical knowledge. In many of these important drug groups, there are already a large number of fairly

similar drugs. As the gaps in biomedical knowledge decrease, so do the opportunities for the development of new or useful related drugs. This is, as plainly as shown in Figure 2, an international phenomenon. This does not reflect a loss of innovative capacity, but rather reflects the normal course of a growth industry as it becomes technologically more mature.

Another factor could be that in American medicine, basic research on fundamental problems in biology often is attributed as having a higher status prestige-wise than applied research in therapeutics. As a result, the number of highly talented investigators attracted into the drug research field may not be as high as would be desirable.

On the other hand, clinical pharmacology and therapeutics as academic disciplines appear to be stronger in certain other countries, particularly Sweden and the United Kingdom. This fact and the availability of high-quality drug-oriented investigators in these countries may also be stimulating the shift of early clinical trials from the United States to these countries.

I would now like to turn to the next factor which, in our judgment, has had an important effect on drug development in the United States.

DIFFERENCES IN DRUG LAWS AND REGULATIONS BETWEEN NATIONS

Mr. Chairman, an ideal regulatory system should carefully review each new drug, screen out the ineffective drugs, evaluate benefit-risk data and approve as rapidly as practical those drugs which represent new or useful modes of treatment.

With that in mind, let us examine how drug regulatory systems can affect the drugs available in a country. Drug firms respond to the same economic forces that affect other commercial enterprises, including the cost of complying with regulatory requirements. Major firms developing new drugs in the western world are almost all multi-national in character. They can therefore develop and market their products wherever costs are less and regulations less stringent. This may result in earlier availability of drugs in some countries. In some cases, the cost of development could prevent development of a drug entirely if expected sales are not large. This may often be the case for drugs to be used for treating a rare condition.

Drug regulatory systems vary widely from country to country. Most include a requirement that drugs be safe. Some include effectiveness requirements, while others do not. Some regulate all phases of drug investigation in humans. Some regulate only part of this process, while others do not regulate investigation at all. There are thus many opportunities for multi-national drug firms to investigate and market drugs under widely differing regulatory systems.

This country is the first drug-developing Nation to attempt to establish the effectiveness of its entire supply of prescription drugs, both old and new. Our drug efficacy study of the effectiveness of drugs marketed between 1938 and 1962 is unique in world medicine, and is serving as a model for increasing numbers of other nations, which I assure you are imitating us.

Even so, most countries are not as yet keeping unsafe drugs out of their markets, much less ineffective ones. This fact has recently been pointed out in the Medical Letter through a warning to travelers to South America, and has also been the subject of recent newspaper articles in the Washington Post by Mr. Morton Mintz. (Appendix C)

It is, therefore, clear that the degree to which any country regulates the marketing of drugs within its boundaries has a significant impact on both the number as well as the quality of drugs available to its consumers.

Let us now turn to the fourth factor identified at the beginning of my statement--the 1962 Drug Amendments.

REQUIREMENTS OF 1962 DRUG AMENDMENTS

The Kefauver-Harris Amendments of 1962 represented pioneering legislation which added three extremely important requirements: An effectiveness requirement for all new drugs, control over the research of the drug industry through the IND procedures, and a mandate to regulate prescription drug advertising.

The Effectiveness Requirement

The effectiveness of a drug must be supported by "substantial evidence"--based on adequate and well-controlled investigations, including clinical trials conducted by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved. This requirement for well-controlled clinical trials was supported unanimously by a wide variety of leading scientists, physicians, and clinical investigators who testified at the Kefauver hearings. There was general agreement that reliance on the subjective impressions of even highly qualified observers was not an adequate substitute for such studies and could not provide an objective basis for decisionmaking.

There is no doubt that an effectiveness requirement will decrease the number of drugs marketed in a country and can delay the marketing of others. Since the United States is one of a small number of countries to have an effectiveness requirement, it is logical to expect that more drugs will be marketed in countries without the requirement. As you know, the 1962 Amendments required FDA to review the effectiveness of all prescription drugs marketed between 1938 and 1962, during which years they had only to be "safe." As a result of this review we have removed more than 700 different drug products from the market for lack of effectiveness. Many of these are still available in other countries but we are well rid of them.

Both physicians and economists have recently challenged the benefits of having an efficacy requirement; although I find it hard to believe they can be serious. They contend that the cost to society of delaying important new drugs while their effectiveness is proved is greater than the benefits produced by the avoidance of ineffective drugs. A full discussion of this argument is beyond the scope of this testimony, but it is worth citing a recent example of an extremely costly failure to establish effectiveness.

The example is the use of diethylstilbestrol (DES) in pregnancy to prevent spontaneous abortion. This treatment was widely practiced in the 1940's and 1950's, although its effectiveness was never established through well-controlled studies. It was apparently considered safe by all reasonable standards, but in 1971, Dr. Arthur Herbst showed that the female children of mothers treated with DES had a markedly increased incidence of vaginal cancer at puberty. The cost to society in either anguish or dollars can never be totaled. One could suggest in retrospect that the safety of DES had not in fact been adequately demonstrated, but that is the wisdom of hindsight. It would have taken a remarkable prescience to know that treatment of a mother could result in a malignancy in her child 15 to 20 years later. We can never hope to guarantee the absolute safety of any drug, but we can determine whether it is effective. The DES disaster resulted from widespread use of a drug that was ineffective and was easily demonstrated to be ineffective once

controlled trials were attempted. We are used to considering risk-benefit ratios when an effective drug has known or potential hazards. The DES case is a reminder that where there is no benefit, the risk-benefit ratio is always unacceptable. Fortunately, ineffective drugs do not generally turn out to have hazards of this magnitude, but the possibility exists, and the marketing of drugs without documented effectiveness courts unnecessary disaster.

Some have argued that although the effectiveness of a drug is important, it can be properly appraised in clinical practice and that Federal restrictions on the availability of drugs are unnecessary and represent judgments that are properly left to the physician. I have great respect for practicing physicians and the practical problems they face in everyday practice, but I cannot agree that effectiveness can be reliably established in the course of medical practice or that the FDA requirements for proof of effectiveness represent an undue limitation on the practice of medicine. In fact, the exact opposite appears to be the case. The practice of medicine is strengthened when the therapeutic options available to the physician are all known to be effective. Medical practice is difficult enough without the physician having to worry about the basic effectiveness of the drugs he prescribes.

I think that most physicians believe this, and that the present attack on the effectiveness requirements represent a response to the unavailability in this country of a relatively small number of drugs that physicians feel are particularly important.

I believe that better understanding of the effectiveness requirement would result in greater appreciation and acceptance of it. Much of the debate with industry over this requirement subsided when FDA published in 1970 regulations describing exactly what a well-controlled study was. Uncertainty over the meaning apparently was as much a cause of the dispute as the requirement itself.

We recognize that certain drugs of therapeutic merit have become available in foreign countries before they have become available in the United States. However, we do not agree that a change in the effectiveness requirement is a responsible solution to this problem.

Investigational New Drugs

Under the Federal Food, Drug, and Cosmetic Act, a new drug may not be shipped in interstate commerce without an approved new drug application (NDA). FDA approves an NDA if adequate and well-controlled data establish that the drug is safe and effective for the conditions recommended in its labeling.

Under the 1962 Amendments investigational use of drugs is also permitted so that sponsors may develop the data needed to demonstrate safety and effectiveness.

The investigations must be scientifically sound and may not expose the subjects to undue hazard. The investigational plan, along with results of animal studies is submitted to FDA for review as a "Notice of Claimed Investigational Exemption for a New Drug," more commonly referred to as an "IND."

The IND is a unique feature of regulatory law which has had enormous impact on new drug development and indeed on clinical research throughout the world. While some other countries also have regulatory requirements over clinical investigation--notably Canada, the United Kingdom, Australia, and the Scandinavian countries--many nations have little or no control over the clinical investigation of new drugs. This is the current situation in, for example, Germany, France, Italy, and Switzerland. This world situation obviously provides a variety of opportunities for a multi-national drug industry to investigate new drugs outside the reach of a strong regulatory process.

It is true that many, if not most drugs initially tested in man, fail to be marketed because of a lack of effectiveness or because of adverse effects, or a lack of commercial interest and never progress beyond an early stage of investigation. It is, therefore, particularly tempting to perform initial tests of drugs in countries that do not regulate such early clinical testing. We suspect that our IND procedures have been an important factor in the shift of early drug research toward Europe. It is, nevertheless, difficult to imagine that we could return to the days in which the safety of investigational subjects depended solely on the responsibility and knowledge of clinical investigators. The IND regulations assure that both adequate animal studies are conducted prior to clinical testing and that proper monitoring and precautions are followed in clinical trials.

Criticism of the IND process has centered not on its existence, but on its management and on specific requirements that are thought to be excessive or scientifically incorrect.

Another limiting factor we have discovered has been an apparent tendency to give the review and monitoring of investigational plans a lower priority than the review of completed studies. This has resulted all too frequently in poor research planning and the use of poor study procotols so that redundant studies were performed and important questions not addressed. At present all data relating to a new drug are not assembled for review until the NDA is submitted. The result is often an application of great bulk, representing considerable effort, but with important deficiencies that should have been addressed at an earlier stage of investigation.

It is now clear that the key to improving the drug development process in this country, and to better assuring the public safety, is to give primary attention to planning and review during the investigation phase of new drug development. Such a refocusing of our efforts is already happening, and it is requiring a very important, but subtle, change in the attitude of the Agency regarding its role in the development of drugs. In the past, the planning of investigational studies has been viewed as the responsibility of industry, and the conduct of these studies as the responsibility of the investigator. Concurrently, FDA viewed its

primary commitment in reviewing IND's to assuring the safety of the proposed studies without being involved in the design of the study. Such a policy would assure that we did not compromise our ability to review a study in an unbiased fashion when the results were presented. This policy was also reflected in the Agency's reluctance to state, in the form of guidelines, the kinds of studies required for various drug classes.

While this desire to separate the role of study design from the role of study review is not without merit, a strict separation has two important negative consequences. First, some clinical investigations will be carried out when they cannot on their face succeed in providing acceptable data. In such cases, investigational and financial resources are wasted and, most important, patients are needlessly subjected to the inconvenience and possible hazards of a worthless trial. The second consequence is that drug development can be delayed. To the extent that a drug is useful, such a delay represents a cost without corresponding benefit to society.

Recognizing these consequences, the FDA has recently begun to modify its approach. While there can be no question that a study must in the end stand or fall on its merits, it is our present policy to provide guidance at an early stage of study design, to assure that clinical investigations are well-designed and can meet regulatory requirements. This is being accomplished through meetings between manufacturers and the Agency at which specific phases of the IND process and investigational plans are discussed.

In addition, we are developing, with the help of numerous experts from the medical community and industry, guidelines for clinical studies for a number of drug classes. Some of these guidelines are now available in draft form and others will be in the near future.

Full implementation of a new policy focusing on the IND phase will require extensive revision of the new drug regulations. We anticipate the proposed revisions will be ready for publication by the end of the fiscal year. Other proposals will also address certain issues not well handled by the old regulations, such as the monitoring of clinical investigation and the followup of patients in those cases when unforeseen toxicity or potential toxicity occurs.

In sum, the proposed revision of the new drug regulations will codify the best procedures and take advantage of our experience in improving old regulations. Any impact of the new regulations on the rate of new drug approvals will of course not be demonstrable until several years after the regulations go into effect. We would hope, however, that once the regulations are in effect the time from drug discovery to approval will be substantially shortened for those agents which meet the essential standards of safety and effectiveness. These regulations cannot make the United States as "easy" a country to develop drugs in as a country which does not regulate drug investigation at all. Even FDA critics have not advocated elimination of the IND regulations; rather they have hoped for greater responsiveness and flexibility. I believe this can be accomplished.

Regulation of Drug Advertising

The 1962 Amendments also directed the Food and Drug Administration to regulate prescription drug advertising. This is again a more stringent requirement than in other countries. One need only look at the advertising in a medical journal in Britain, for example, to determine for himself which country does a better job of promoting full disclosure and fair balance in advertising.

Nevertheless, the effect on the introduction of new pharmaceuticals must be appreciated. In the United States, our regulations require that advertising claims be limited to claims made in the labeling. Of course, the label claims must be approved by FDA and supported by substantial evidence of effectiveness.

Since manufacturers frequently want to make specific claims about therapeutic advantages regarding either safety or effectiveness of their particular drug, the precise wording of the labeling (package insert) may take on considerable importance. When a manufacturer, in his proposed package insert,makes claims which FDA feels are not supported by available data, protracted controversy between the manufacturer and the Agency may ensue over the wording of the label. This, of course, may delay the introduction of a new drug.

In summary, it should be recognized that these three important features of the 1962 Amendments are pioneering requirements in world regulatory law. These features of United States law are

becoming more common in other countries. The effectiveness requirement in particular is being adopted by more and more nations, the latest being the United Kingdom, in 1972. In addition, an increasing number of drug developing countries are adopting controls over human research. Many governments in smaller nations, particularly the developing nations, depend upon FDA judgments in their own evaluations of drugs. Despite the controversy the requirements have generated, we firmly believe they are right, and under effective management they will not unnecessarily hamper the development and introduction of important new drug entities in this conntry.

IMPLEMENTATION OF 1962 AMENDMENTS

When the 1962 Amendments were enacted, neither the industry nor the Agency had the management systems, the personnel, or the sophistication to accomplish the scientific leap forward envisioned by that new legislation. Both struggled with limited resources, all too often in an unfortunate atmosphere of acrimony. The academic community and clinical investigators remained primarily interested in basic biological research and were generally little interested in developing the quality information in support of new drugs which all of us want to see.

In 1969 the Food and Drug Administration underwent a major reorganization and subsequently took a number of steps to address its management and resource problems. A modern project management system was established, new scientific and managerial talents were brought to the Agency, and substantial budgetary support was provided by the Administration. The decisionmaking process was progressively opened to broader scrutiny and influence of greater scientific expertise through the use of outside consultants and advisory committees. By 1972 a scientific advisory committee system was beginning to be associated with the actual drug review process and this system is now functioning with 15 committees fully established. Each committee provides its judgments, after detailed review of the application by the FDA staff, on most of the NDA's for new chemical entities that fall within its area of expertise.

A detailed study of the paperwork and data processing aspects of the drug review process was conducted by Auerbach Associates; the implementation of their recommendations began in 1973 and is still ongoing. These developments and a variety of procedural changes have improved both the efficiency of the review process and the scientific quality of FDA decisions.

For over three years the safety review of every IND has been conducted within the required 30 days. The backlog of NDA's not reviewed within the statutory limit of 180 days has been halved in the past year and now stands at 13 (there were about 250 NDA's submitted in 1973). The total number of new molecular entities approved in 1973 was 18, the highest since 1967 (Appendix A).

We believe the record of the past five years will show that the Agency has taken serious recognition of its management problems and taken important steps toward their solution. This has been accompanied by an increase in the quality of New Drug Applications submitted to us and in the clinical data supporting safety and effectiveness. All of our old problems are not solved, but we believe that processing time by the FDA is becoming less of a factor in delaying the introduction of new drugs and that improvements will continue.

I personally believe that at present, our drug laws and regulations provide proper balance of patient protection and encouragement of drug development and that the improvements in the functioning of the regulatory system, which I have described, will facilitate drug development without having any detrimental effect on public safety.

We are about to publish final regulations indicating that the FDA will accept data from foreign countries in support of New Drug Applications, providing such data meet United States standards of scientific quality and the ethical standards of the Doctrine of Helsinki. We believe this will have a favorable impact, both in stimulating quality research in Europe and in minimizing any time delays in utilizing such data in New Drug Applications in the United States.

Drug research under our current regulations has a long record of productivity and a good record of safety. This is to be expected since such research is conducted by experts whose data are subject to the scrunity of their scientific colleagues and of the FDA. Research on new drugs is, and should be, carried out under the same ethical standards and institutional review procedures that apply to all human investigation.

The evaluation of new drugs probably involves less risk to patients participating in clinical trials than is commonly recognized. The most critical period in the lifetime of a drug is in the first year or two after marketing. During this period, there is widespread use of the drug in medical practice, as compared to use during the investigational phase, and serious unforeseen adverse reactions, if they are going to occur, are generally recognized at this time. From the public health point of view, there are more adverse reactions from the known toxicities of marketed drugs than there are from the unsuspected hazards of investigational drugs. Improved usage of marketed drugs in medical practice offers far more opportunities for health gains than improving the usage of investigational drugs. This is not to say that investigators, monitors in industry, or reviewers in the FDA cannot improve their performance, or that we can relax our vigilance in studying new, potentially toxic agents.

SUMMARY

In sum, it is clear that the rate of drug introduction into the United States has slowed since the 1950's. This slowdown is worldwide, but is somewhat greater in this country than in other advanced countries. There appears to be some drugs unavailable in this country that represent modest but real therapeutic gains. We are concerned about this and want to be very sure that useful drugs are not held back unnecessarily. It also appears that drug research has moved abroad to some extent. We are also concerned about this, because of its negative impact on the development of good clinical investigation in therapeutics and because it will further delay the availability of useful drugs.

I think it is also clear that regulatory requirements are an important influence on the availability of new drugs in this country. The law intended this by setting exacting standards for the effectiveness and safety of new drugs. The FDA has always attempted to administer this law honorably and vigorously. And when faced with difficult decisions, we will knowingly err in the direction of assuring safety. We believe the record since 1962 speaks for itself. There have been no major drug disasters in this country with either marketed or investigational drugs since the Kefauver-Harris Amendments.

Many ineffective and unsafe drugs have been removed from the market. Yet, the drug industry has maintained a continuing supply of important new drugs to the medical profession and the public, and it has also maintained its innovative capacities and scientific vigor.

Nevertheless, any delay in the introduction of important new drugs which can be avoided by better research, better planning, and better administration of the FDA is in the public interest. We believe we have done much in recent years to recognize and correct problems in our own house which have contributed unnecessarily to delaying decisionmaking on new drugs. And we anticipate continuing improvements in the future.

Today, the Agency is improving its managerial systems and scientific competencies, and it has opened the decisionmaking process to public scrutiny. We are also seeing a steady improvement in the quality of applications received, especially from large experienced drug firms, and steady improvements in the quality of clinical trials. We anticipate further gains will be made as additional administrative and policy changes focus still greater attention on the IND phase of the drug development process.

We suspect that many critics who have voiced concern over the drug laws have, in reality, been dismayed by management problems in the FDA or in industry, or are stating their own disagreement with a particular individual or Agency judgment. We accept these criticisms as sincere, but misguided, for we believe that the vast majority of physicians and scientists recognize that the Federal Food, Drug, and Cosmetic Act, with its requirements for effectiveness, safety and the IND process, is in the public interest.

Finally, we would emphasize that the Agency is engaged in far more than approving the introduction of new pharmaceuticals. The FDA is unique among drug regulatory agencies in the world in conducting a review for effectiveness of all marketed prescription drugs, old drugs as well as new drugs, and an equally comprehensive review of the safety and effectiveness of all over-the-counter drug products.

We believe an overall appraisal of our system should recognize the important fact that our goal is not simply to have new drugs ahead of everyone else. It is to have the finest possible total armamentarium of therapeutic agents. While we may not be introducing certain new drugs into this country quite as rapidly as certain other countries, we believe we are well ahead of most other nations in achieving this overall goal.

We are convinced that the fundamental strategy of drug regulation in the United States is sound. There is an absolute need for a technologically innovative nation to have firm societal control over the chemicals marketed for use by humans as therapeutic agents and over the chemicals introduced into human investigation. We believe those concerned about delays in the introduction of important new pharmaceuticals in this country are fundamentally misguided if they seek to correct that situation by altering the effectiveness requirement in the law.

We will be pleased to respond to any questions the Subcommittee may have.

Appendix A

YEARLY INTRODUCTION OF NEW DRUG PRODUCTS
1950-73

The data in these lists are derived from FDA files and from the publications of Paul de Haen. FDA believes that the list represents the most accurate data available to date, but there may be a small number of errors remaining, particularly in the 1950's. Like the lists of Paul de Haen, these lists contain drug products that are new salts or esters of previously marketed drugs(N). New dosage forms, etc, are not generally included unless they involve a new salt or ester. In some cases a drug available for many years was first approved in the 1950's, in which case it is listed (e.g. acetaminophen, 1950).

In evaluating the degree of therapeutic gain arising from the availability of a new drug, FDA considered only the degree of therapuetic gain deemed to have been offered by the drug at the time of its introduction, considering available therapeutic alternatives at the time, without reference to subsequent experience or current status. Thus, certain drugs no longer marketed may be designated as representing important gains. Our criteria were:

A. Important Therapeutic Gain - Drug may provide effective therapy or diagnosis (by virtue of greatly increased efficacy or safety) for a disease not adequately treated or diagnosed by any marketed drug, or provide markedly improved treatment of a disease through improved efficacy or safety (including decreased abuse potential).

B. Modest Therapeutic Gain - Drug has a modest, but real advantage over other available marketed drugs; e.g., somewhat greater effectiveness, decreased adverse reactions, less frequent dosing in situations where frequent dosage is a problem, etc.

These evaluations are tentative, pending further study which is in progress. Ratings given here are, for the most part, by Bureau of Drugs personnel, and are being refined through consultation with authorities in various fields. We are aware that many specific ratings will be controversial, but we believe that the present ratings are useful beginnings. In any case, the ratings are available for criticism and comment and it is possible for any analyst to develop his own lists of important, modest, and no-gain drugs.

1950

DRUG NAME	RATING
Acetaminophen	
Acetoxan	
Alkavervir	A
Amphetamine PO_4 Dibasic (N)	
Biphenamine HCl	B
Corticotropin	A
Cortisone Acetate	A-
Cyclamate Sodium	B
Dicyclomine HCl	
Dimethyl Tubocurarine Cl (N)	
Disodium Tetrathiodiglycolate	
Ethyl Biscoumacetate	
Khellin	
Levararterenol Bitartrate	B
Mercumatilin	
Methafurylene Br (N)	
Methafurylene Fumarate (N)	
Methantheline Br	
Methdilazine Hydrochloride	
Methimazole	B
2-Methoxymethyl-5-Nitrofuran	
Morpholinium Ethosulfate	
Octriphonate ANTI	
Octyl Nitrite (N)	
Oxytetracycline HCl (N)	
Oxytetracycline	
Pipenzolate Br.	
Piperazine Estrone	
Polycarboxylic Exchange Resin	
Potassium P-amino Benzoate (N)	A
Pregnenolone	
Pregnenolone Acetate (N)	
Procainamide HCl	A
Promethazine HCl	B
Pyrabrom	
Quinidine Gluconate (N)	
Racemorphan HBr	
Salicylazosulfapyridine	A
Sodium Gentisate	
Sodium Secobarbital (N)	
Sodium Thiamylal	
Thiocarbasone	
Vitamin A Palmitate (N)	B
Zirconium Carbonate	

1951

DRUG NAME	RATING
Aminopterin Sodium	A
Benzoquinonium Cl	
Bromaleate	
Bromazine HCl	
Bromdiphenhydramine HCl (N)	
Calcium Aminosalicylate (N)	
Caramiphen Edisylate	
Carbacrylamine Resins	
Chlorotrianisene	
Cyclocumarol	
Dextran	A
Diamthazole	
Diethylpropanediol	
Hydergine	
Dimethisoquin HCl	
Dioxyline PO4	
Diphemanil Methyl Sulfate	
Disodium 5-(P-Sulfophenylazo) Salicyl	
Disulfiram	A
Dyphylline	
Edrophonium Cl	B
Evans Blue	A
Ferrocholinate (N)	
Gallamine Triethiodide	B
Glamylol	
Hexylcaine HCl	
Hydrocortisone Acetate (N)	
Inositol Hexanitrate (N)	
Iopanoic Acid	A
Iothiouracil Sodium	B
Meparfyrol	
Metaraminol Bitartrate	B
Methandriol	B
Methorphiran HBr	
Morphine PO4, Monobasic (N)	
Neomycin SO4	A
Penicillin G Benzathine USP	B
Penicillin G 1-Ephenamine (N)	
Penicillin O Potassium (N)	B
Pentaerythritol Tetranitrate	
Phenacemide	B
Phenacridane Cl	
Phenindione	
Phenyltoloxamine Citrate	

1951 (Con't)

DRUG NAME	RATING
Pituitary Hormone, Posterior	A
Polymyxin B Sulfate	A
Primaquin PO4	A
Probenicid	A
Salicylamide	
Selenium Sulfide	A
Streptokinase Streptodornase	B
Sulfisomidine	
Testosterone Cypionate	B
Trypsin	
Veratrum Viride	

1952

DRUG NAME	RATING
Amylose Triiodide, Beta	
Arsthinol	
Beclamide	B
Bone Marrow, Deproteinized	
Carbazochrome Salicylate	
Chlormerodrin	
Cobra Venom Sol	
Digalloyl Trioleate	B-
Direct Sky Blue Inj.	
Erythromycin	A
Estradiol Cypionate	
Hexamethonium Cl	A
Hydralazine HCl	A
Hydrocortisone (N)	A
Isoniazid	A
Leucovorin	A
Medrylamine	
Methallenestril	
Metharbital	
Methscopalamine Br	
Monobenzone	A
Nalorphine HCl	A
Oxyphenonium Br	
Pamabrom	
Penethamate HI	
Penicillin O Chloroprocaine (N)	
Phentolamine Mesylate (N)	A
Phentolamine HCL	A
Phenylbutazone	A
Promoxolane	
Pyrrobutamine	
Simethicone	
Strontium Lactate	B
Succinylcholine Cl	A
Succinonitrile	
Sulfamethizole	
Tetraglycine Hydroperiodide	
Trichloroethylene	B
Trolnitrate PO4	
Tyloxapol	

1953

DRUG NAME	RATING
Acetazolamide	A
Acetyl Sulfisoxazole (N)	
Alseroxylon	
Aminopentamide	
Benoxinate	
Bithionol	
2-Ethyl Butyl Alcohol	
Calcium Alginate (N)	
Calcium Disodium Edetate	A
Carbinoxamine Maleate	
Cryptenamine Acetates	
Cyclamate Ca (N)	B
Cyclizine HCl	
Cyclopentolate	
Cyclopentolate HCl (N)	
Cycrimine HCl	
7-Diethylaminoethyl Theophylline	
Dihydroxy Al Sodium Carb.	
Dimethicone	B
Diphenylpyraline HCl	
Erythromycin Ethylcarbonate (N)	
Erythromycin Gluceptate (N)	
Ethopropazine HCl	
Ethyl Vanillate	
Ferrous Ca Citrate (N)	
Fumagillin	
Hexamethonium Cl Dihydrate (N)	
Hexamethonium Br (N)	
Hydroxystilbamide Isethionate (N)	
Iophenoxic Acid	
Isomethadone	
Isomethadone	
Levorphanol	B
Lututr[illegible]	
Meclizine HCl	
Mepiperphenidol	
Mercaptopurine (N)	A
Merethoxylline Procaine	
Methotrexate	B
Nitrofurantoin	A
Penthienate Br	
Phenoxybenzamine HCl	B
Phensuximide	B
Piperazine Citrate	A
Piperazine Hexahydrate (N)	
Piperidolate HCl	
Pramoxine HCl	

1953 (Con't)

DRUG NAME	RATING
Procaine Isobutyrate	
Propantheline Br	
Propionate Sodium	
Proparacaine HCl	
Protoveratrines A+B	
Protoveratrines Maleate (N)	B
Pyrimethamine	B
Quercetin	B
Quinine Carbacrylic Res	
Rauwolfia Serpentina	
Reserpine	A
Roloxamine	
Sodium N-Lauroyl Sarcosinate	B
Stanalone	
Stilbamide Isethionate	B
Testosterone Enanthate (N)	B
Tetracycline HCl	
Thyrotropin	A
Tocamphyl	
Tolonium Cl	
Tricyclamol Cl	
Tricyclamol SO4 (N)	
Triethylenemelamine	A
Undecylenate Calcium (N)	
Viomycin SO4	A

1954

DRUG NAME	RATING
Acetyldigitoxin (N)	
Aluminium Hydroxide Gel, Dried (N)	
Aminometradine	B
Aminosalicylate Potassium (N)	
Azapetine HCl (N)	
Azapetine PO4	
Benzomethamine Cl	
Betazole	B
Benztropine Mesylate	A
Bialamicol HCl	
Buclizine HCl	
Busulfan	A
Chlorpromazine HCl	A
Cryptenamine Tannates (N)	
Cyclizine Lactate (N)	
Deslanoside	
Dextran 70	B
Dextromethorphan HBr	B
Digoxin	
Domine	
Ectylurea	
Erythromycin Stearate (N)	B
Erythromycin Lactobionate (N)	
Estradiol Valerate (N)	
Ethiodized Oil	B
Fludrocortisone Acetate (N)	
Fludrocortisone	A
Glaucarubin	
Glutethimide	B
Heptabarbital	
Hydrocortisone Butyl Acetate (N)	B
Laudexium Methyl SO4	
Levothyroxine Na	B
Meclizine di HCl (N)	
Meglumine Iodipamide (N)	A
Mephenesin Carbamate (N)	
Methoxsalen	A
Methscopalamine Nitrate (N)	
Nitroglycerin (N) (sustained form)	
Nystatin	A
Oxtriphylline	
Penicillin G-Hydrabamin (N)	B
Penicillin Phenoxymethyl Hydr	B
Pentolinium Tartrate	B
Piperazine Tartrate (N)	

1954 (Con't)

DRUG NAME	RATING
Pipradrol HCl	
Povidone	
Primadone	B
Propyl Iodone	B
Protoveratrines (N)	
Selenium Sulfate (N)	
Talbutal	
Testosterone Phenylacetate (N)	B
Tetracycline (N)	
Tetrahydrozoline	
Tetrahydrozoline Hydrochloride (N)	
Tridihexethyl Chloride	
Tridihexyl Iodide (N)	
Trimethaphan Camsylate	A
Warfarin Na	

1955

DRUG NAME	RATING
Alkofanone	
Aminitrazole	
Azacyclonol HCl	
Butyl Alcohol	
Carbetapentane Citrate	
Carboxypolymethylene	
Chlorbetamide	
Chlorprocaine HCl	
Chymotrypsin	
Corticotropin Zn Hydroxide (N)	B
Dapsone	A
Dioctyl Na Sulfosuccinate	B
Diphenedione	
Diprotrizoate Sodium	B
Dyclonine HCl	
Ethchlorvynol	
Ethinamate	
Ethoheptazine	
Ethyl Vinyl Ether	
Furazolidone	B
Gitalin	
Hexaflourenium Br	
Hexetidine	
Hydrocotisone Cypionate (N)	
Hydrocortisone Sod. Succinate (N)	
Hydroxychloroquine SO4	
Hyroxydione Sodium	
Iproniazid PO4	A
1-Isonicotinoyl 2-Salicyldenehydrazine	
Meprobamate	B
Methotrexate Na (N)	
Methylphenidate	
Methyprylon	
Methamoctol	
Monoxychlorosene	
Nylidrin HCl	
Penicillin, Phenoxymethyl (N)	
Pentaerythritol Chloral (N)	
Piperazine Ca edetate (N)	
Prednisone	B
Prednisolone Acetate (N)	
Prednisolone	
Procyclidine HCl	
Propoxycaine HCl	
Pyrazinamide	B
Pyridostigmine Br	
Pyrvinium Cl	A
Relaxin	
Senna Concentrate (N)	

1955 (Con't)

DRUG NAME	RATING
Silicofluoride Sodium (N)	
Silver Mannuronate (N)	
Sodium Diatrizoate	B
Stannous Flouride (N)	B
Tall Oil	
Tanphetamine	
Tellurium Dioxide	
Vitamin B 12 w/Intrinsic F (N)	

1956

DRUG NAME	RATING
Acetyl Strophanthidin	
Ambenonium Cl	
Amisometradine	B
Anileridine HCl	
Brompheniramine Maleate	
Calcium Benzoylpas	
Carbocloral	
Chlorisondamine	
Chlorquinaldol	
Clindinium Br	
Cobalamin Conc.	
Cycliramine Maleate	
Cycloserine	A
Cycloserine Tartrate (N)	
Deoxyribonuclease	
Dextriferron	
Di Hexamethylenetetramine Thiocyanate	
Dioxytetracycline Calcium	
Dipipanone HCl	
Disodium Edetate (N)	
Drocode	
Epinephrine Bitartrate	
Ethanolamine Hydroflouride	
Ferroglycine SO4 (N)	
Ferrous Fumarate (N)	
Fructose (N)	
Hydrocortamate HCl	
Hydrocortisone Hemisuc (N)	
Hydroxyprogesterone Caproate	
Hydroxyzine HCl	
Levallorphan Tartrate	
Liothyronine Na	B
Mepenzolate Br	
Methitural Na	
Monosodium L-glutamate	A
Norethandrolone	
Novobiocin Calcium (N)	
Novobiocin Sodium	A
Oleandomycin	
Pancreatin Dornase	
Phenmetrazine HCl	B
(Phenylthio) Acetic Acid	
Povidone - Iodine	B
Prochlorperazine Maleate	A
Promazine HCl	
Rescinnamine	
Sulfaethiodole	B
Thenalidine Tart	
Theobromine Mag. Oleate	
Thiram	
Trisodium Edetate (N)	
Zoxazolamine	

1957

DRUG NAME	RATING
Acenocoumarol	
Acetyl Sulfamethoxypyridazine (N)	A
Amphotericin B	B
Azuresin	
Bemegride	
Benzactyzine HCl	
Benzene Hexachloride	A
Bisacodyl	
Cadmium Sulfide	
Calcium Kinate Gluconate	
Chlorambucil	A
Chlorothiazide	A
Chlorothiazide Sodium (N)	
Coconut Oil (Diolamine Condensate)	
Deserpidine	
Dexpanthenol (N)	
Diiodohydroxyquin	B
Dimethoxanate HCl	
Ethotoin	B
Ethoxzolamide	
Florantyrone	
Fenticlor	B
Hexocylium	
Homarylamine HCl	
Hydroxyprogesterone Acetate (N)	
Insulin Zn Susp (N)	B
Iron Dextran Inj (N)	B
Isobutylsalicyl Cinnamate	
Isopropamide Iodide	
Isothipendyl	
Isothipendyl HCl (N)	
Levamfetamine Alginate	
Mecamylamine HCl	B
Meglumine Diatrizoate (N)	
Mepazine Acetate (N)	
Mepazine HCl	
Mestranol	
Methocarbamol	
Methsuximide	B
Methylprednisolone (N)	
Norethindrone	A
Norethynodrel	
Orphenadrine HCL	
Oxanamide	
Penicillinase	
Penicillin O-Sodium (N)	
Perphenazine	
Phenaglycodol	

1957 (Con't)

DRUG NAME	RATING
Phenprocoumon	
Phenyltoloxamine HCl (N)	
Piperazine (N)	
Piperazine PO4 (N)	
Poloxalkol	
Polyestradiol Phosphate	
Prednisolone Butyl Acetate (N)	
Prednisolone Sodium Phosphate (N)	B
Prochlorperazine (N)	
Prochlorperazine Esylate (N)	
Prochlorperazine Edisylate (N)	
Propethyleneoxides	
Propiolactone	B
Propoxyphene HCl	B
Ristocetin	B
Safflower Oil	B
Sulfalene	
Sulfamethoxypyridazine	B
Thiopropazate	
Tolbutamide	A
Triacetin	
Triamcinolone	B
Tridihexethyl Cl	
Triflupromazine HCl	

1958

DRUG NAME	RATING
Arginine L Hydrochloride	A
Atropine Tannate (N)	
Benzonatate	
Bunamiodyl Sodium	
Captan	B
Captodiame Hydrochloride	
Carbetapentate Tannate (N)	
Chlormezanone	
Chlorohexidine HCl	
Chlorpropamide	B
Chlorzoxazone	
Cyclandelate	
Deanol	
Deanol Acetamido Benzoate (N)	
Dexamethasone	B
Dichlorphenamide	
Dithiazanine Iodide	
Domiphen Bromide	
Erythromycin Estolate (N)	B
Erythromycin Ethylsuccinate (N)	
Ficin	
Fluoxymesterone	B
Fluroxene	
Halothane	A
Heparin Potassium (N)	
Hexocyclium Methylsulfate (N)	
Hydroxyzine Pamoate (N)	
Iodipamide Meglumine	B
Kanamycin Sulfate	A
Piperazine Gluconate (N)	
Pipethanate Hydrochloride	
Polystyrene Sulfonate Sodium	A
Protokylol Hydrochloride	
Protoveratrine A (N)	
Styramate	
Sulfadimethoxine	
Syrosingopine	
Triamcinolone Acetonide (N)	
Triethanolamine Polypeptide Oleate Conc. (N)	B
Trifluoperazine Hydrochloride	
Triflupromazine	
Trimeprazine Tartrate	
Triprolidine Hydrochloride	
Troleandomycin (N)	
Valethamate Bromide	

1959

DRUG NAME	RATING
Amberlite Ira-401	
Anisindione	
Arginine Glutamate (N)	
Biperiden HCl	
Bendroflumethiazide	
Carbaspirin Calcium	
Carisoprodol	
Chloramphenicol Na Succinate (N)	
Chlorphenoxamine HCl	
Choline Salicylate (N)	
Chloridanol	
Clemizole	
Clemizole HCl (N)	
Cyclophosphamide, Anhydrous	A
Demecarium Bromide	
Dexamethasone Acetate (N)	
Dexamethasone Na Phosphate (N)	
Dexbrompheniramine Maleate	
Diethylpropion	B
Dioctyl Calcium Sulfosuccinate (N)	
Echothiophate Iodide	
Fibrinolysin, Human	
Flumethiazide	
Fluormetholone	
Fluphenazine Hydrochloride	
Furaltadone	
Griseofulvin	A
Griseofulvin Microcrystalline (N)	B
Hexadimethrine Bromide	B
Hydrochlorothiazide (N)	
Hydrocortisone Na Phosphate (N)	
Hydroflumethiazide	
Imipramine HCl	A
Indocyanine Green	B
Isocarboxazid	
Isosorbide Dinitrate	B
Isoxsuprine HCl	
Medroxyprogesterone Acetate Inj.	B
Methazolamide	
Methoxypromazine Maleate	
Methyl-2(Diethyl Acetyloxy) Benzoate	
Methylprednisolone Acetate (N)	
Methylprednisolone Na Succinate (N)	
Nandrolone Phenpropionate	
Nialamide	
Orphenadrine Citrate (N)	
Oxymorphone	B
Oxymorphone HCl (N)	
Oxyphenisatin	

1959 (Con't)

DRUG NAME	RATING
Phenazocine Hydrobromide	B
Phenelzine	
Phenethicillin Potassium	
Phenformin HCl	A
Pheniprazine	
Phentermine	
Phentermine Resin Complex (N)	B
Phenyl Aminosalicylate (N)	
Pipamazine	
Polyurethane Foam	-
Prednisone Sodium Succinate (N)	
Prothipendyl Hydrochloride Monohydrate	
Pyrvinium Pamoate (N)	
Rolitetracycline	
Sparteine Sulfate	
Sulfamethazine	
Sulfaphenazole	
Sulfinpyrazone	
Thioridazine Hydrochloride	B
Thiotepa	B
Triamcinolone Diacetate (N)	
Triclobisonium Chloride	
Trihexinol Methylbromide	
Trimethidinium Methosulfate	
Trimethobenzamide HCl	B
Warfarin Potassium (N)	
Xylometazoline HCl	

1960

DRUG NAME	RATING
Aluminum Hydroxychloride	
Aluminum Nicotinate (N)	
Aminoglutethimide	B
Amphenidone	
Bacitracin-Methylene Disalicyl (N)	
Benzphetamine HCl	
Benzthiazide	
Chlophendianol HCl	
Chlordantoin	
Chlordiazepoxide HCl	A
Chloroxylenol	
Chlorphenesin	
Chlorthalidone	B
Copoietin	
Demeclocycline HCl	
Dexamethasone Tebutate (N)	
Dichlorisone Acetate	
Dimethindene Maleate	
Diphenoxylate HCl	B
Emylcamate	
Ethosuximide	B
Fibrinolysin, Bovine (N)	
Fluprednisolone	
Glucagon HCl	A
Guanethidine SO4	A
Hydrocortisone Phosphate (N)	
Isocyclamine	
Lucanthone HCl	A
Magaldrate	
Magnesium Aluminate Sulfate Hydrate	
Mephenozalone	
Mepivacaine HCl	B
Methandrostenolone	
Methicillin Sodium	A
Methohexital Sodium	
Methyclothiazide	
Nitrofurantoin Sodium (N)	
Oxethazaine	
Oxymetholone	
Oxyphenbutazone	
Paromomycin Sulfate	
Pelargonic Acid	
Phenactropinium Chloride	
Phenyramidol	
Piminodine Esylate	

1960 (Con't)

DRUG NAME	RATING
Poldine Methylsulfate	
Polycarbophil	
Polyferose	
Pregnenolone Succ. (N)	
Quinidine Polygalacturonate (N)	
Simethicone	
Spironolactone	A
Trichlormethiazide	
Triparanol	B
Tropicamide	-

1961

DRUG NAME	RATING
Acetophenazine Malcate	
Aluminum Zirconium Chloride Hydrate	
Amitriptyline Hydrochloride	B
Amylase, Alpha	
Aspartate, Potass. & Mg.	
Betamethasone	
Biperiden Lactate (N)	
Bromelains	
Cinoxate	
Colistimethate Sulf.	B
Cyproheptadine HCl	
Dipyridamide	
Dromostanolone Propionate	B
Dydrogesterone	
Epinephryl Borate (N)	
Ethamivan	
Etryptamine Acetate	
Fluocinolone Acetonide	B
Flurandrenolide	
Glycopyrrolate	
Guar Cellupectinoid	
Hydroxyphenamate	
Isoetharine	
Isoetharine HCl (N)	
Isoetharine Mesylate (N)	
Levamphetamine	
Mebutamate	
Metyrapone	A
Metyrapone Tartrate (N)	
Norethindrone Acetate	
Oxyphencyclimine Hydrochloride	
Paramethasone Acetate	
Phendimetrazine Tartrate	
Phentermine HCl (N)	
Polythiazide	
Propiomazine Hydrochloride	
Stanozolol	
Sulfamethoxazole	
Thiethylperazine Maleate	
Tolbutamide Sodium (N)	A
Tranylcypromine Sulfate	B
Vinblastine Sulfate	A
Zinc Pyrithione	B

1962

DRUG NAME	RATING
Amphomycin	
Angiotensin	B
Anisotropine Methyl Bromide	
Bisacodyl Tannex	
Carphenazine Malcate	
Chlorprothixene	
Colistin Sulfate	B
Ethionamide	A
Fluorouracil	A
Hydroxycobalamin	
Hytrast	B
Inositol Niacinate	
Ipodate Calcium (N)	B
Ipodate Sodium	B
Iothalamate	B
Iothalamate Sodium (N)	
Levopropoxyphene Napsylate	
Metaxalone	
Methoxyflurane	B
Methyldopa	A
Methyldopate HCl (N)	B
Methysergide Maleate	A
Nandrolone Decanoate (N)	
Oxacillin Na	B
Oxytocin	B
Phytate Na	
Pipazethate HCl	
Sulfachlorpyridazine	
Tennecetin	A
Uracil Mustard	A

1963

DRUG NAME	RATING
Acetylcysteine	B
Ampicillin Trihydrate	A
Chloral Betaine	
Cyclothiazide	
Diazepam	
Idoxuridine	A
Metronidazole	A
Nonoxyrol	
Oxytocin Citrate (N)	B
Pargyline	
Penicillamine	A
Quinethazone	
Vincristine SO4	A

1964

DRUG NAME	RATING
Acetohexamide	B
Acrisorcin (N)	
Aminocaproic Acid	A
Anileridine	
Candicidin	A
Cephalothin	A
Cephalothin, Sodium (N)	B
Desipramine HCl (N)	
Ethylestrenol	
Flouroethyl	-
Melphalan	B
Methopholine	
Nafcillin Sodium	
Nalidixic Acid	A
Oxandrolone	
Oxymetazoline	
Polysaccharide Iron Complex (N)	
Pralidoxime	A
Pralidoxime Cl (N)	
Quinacrine HCl (N)	
Surgibone	
Triamterene	B
Trioxsalen	
Tromethamide	
Vancomycin Hydrochloride	A

1965

DRUG NAME	RATING
Ampicillin (N)	
Ampicillin Na (N)	B
Bethamethasone Disodium Phos. (N)	
Chlormadinone Acetate	
Chlorphentermine	
Cholestyramine Resin	A
Cloxacillin Sodium (N)	
Dactinomycin	A
Dimethisterone	
Doxapram HCl	
Indomethacin	B
Iron Sorbitex (N)	
Lincomycin HCl	B
Mecamylamine HCl	
Methavalone	
Methixene HCl	
Nortriptyline HCl	
Oxazepam	
Sulisobenzone	
Tolazamide	B
Tolnaftate	A
Tromethamine Inj.	A
Tymbamate	

1966

DRUG NAME	RATING
Acetylcholine Cl	
Allopurinol	A
Amantidine HCl	A
Amopyroquin CHl	
Ampicillin Anhydrous (N)	
Betahistine HCl	
Dipyrone (N)	B
Ethynodiol Diacetate	
Furosemide	A
Gentamycin	A
Methacycline	
Methotrimeprazine	B
Pipobroman	B
Prilocaine	B
Quinaldine Blue	
Sulfameter	
Sulfamethoxydiazine	
Thioguanine Anhy.	B

1967

DRUG NAME	RATING
Bephenium Hydroxynaphthoate	A
Betamethasone Valerate (N)	
Butaperazine Maleate	
Chlordiazepoxide (N)	
Clofibrate	A
Clomiphene Citrate	A
Dextrothyroxine, Sodium	B
Diphenidol	
Doxycycline Monohyd	
Ethambutol, HCl	A
Ethacrynic Acid	
Fluphenazine Enanthate (N)	B
Haloperidol	B
Hydroxyurea	B
Mefenamic Acid	
Methenamine Hippurate (N)	
Pentazocine HCl, Lactate	B
Propranolol HCl	A
Protryptiline HCl	
Tetracycline PO4 (N)	
Thiabendazole	A
Thiothixene	
Triclocarban	

1968

[illegible]	RATING
	A
Carbamazepine	A
Cephaloridine	B
Deferoxamine Maleate	A
Fentanyl Citrate	B
Meprednisone	
Perphenazine	

1969

DRUG NAME	RATING
Cytarabine	A
Doxepin HCl	
Doxycycline Hyclate (N)	
Flumethasone Pivalate	
Mafenide Acetate	A
Medrysone	
Piperacetazine	
Procarbazine HCl	B
Sutilains	B
Testolactone	
Triamcinolone Hexacetonide (N)	
Tyropanoate, Sodium	

1970

DRUG NAME	RATING
Carbenicillin Disod.	A
Clindamycin	B
Cosyntropin Inj.	
Droperidol Inj.	
Flavoxate HCl	
Floxuridine	B
Flurazepam HCl	B
Gluceptate, Calcium	B
Hetacillin	
Ketamine HCl	B
Levodopa	A
Lithium Carbonate	A
Lypressin	A
Menotropine (Pergonal)	A
Mesoridazine	
Mithramycin	A
Mitotane	B

1971

DRUG NAME	RATING
Capreomycin Sulfate	B
Cephalexin Monohyd	
Clindamycin Palamtate (N)	
Flucytosine	A
Fluocinonide	
Haloprogin	B
Megestrol Acetate	
Meglumine Iothalamate (N)	B
Methylmethacrylate	A
Minocycline HCl	B
Naloxone HCl	A
Propoxyphene Napsylate (N)	
Pyrantel Pamoate	B
Rifampin	A
Spectinomycin	B
Thiothixene Inj. (N)	
Tretinoin	A

1972

DRUG NAME	RATING
Bupivicaine	B
Carbachol (Intraocular)	B
Carbenicillin Indanyl Sodium (N)	B
Clorazepate DiPotass	
Desonide	
Dicloxacillin, Sodium	
Enflurance	
Fluphenazine Decanote (N)	
Pancuronium Bromide	B
Polytef Paste	B
Triclofos	

1973

DRUG NAME	RATING
Amoxicillin	
Bleomycin Sulfate	B
Calusterone	B
Cefazolin Sodium	B
Clotermine HCl	
Cromolyn Sodium	A
Diazoxide	B
Fenfluramine	B
Imipramine Pamoate (N)	
Iocetamic Acid	
Mazindol	
Metaproterenol Sulf	B
Metolazone	
Norgestrel	
Prostaglandin F2	A
Silver Sulfadiazine	B
Softconbandage Lens	A
Trimethaprim Sulfamethoxazole	B

APPENDIX B

CURRENT STATUS OF CERTAIN DRUGS MARKETED

OUTSIDE THE U.S.

Particular emphasis has been given by Dr. William Wardell* to differences in the availability of new drugs between the United States and Great Britain, and Mr. Paul deHaen* has identified a number of other drugs of importance marketed in certain countries other than the U.S. Described here is the status in the U.S. of the drugs not marketed in the U.S. that are cited by Wardell and/or deHaen, together with certain other drugs presently under study.

Drugs are separated into those that have and those that have not been studied in the U.S. under an Investigational New Drug exemption (IND), whether the latter is presently active or inactive; the status of study is described for those drugs that have INDs.

The term "approvable NDA" refers to a situation in which the drug sponsor has been informed that he may market after final product labeling is submitted. Ordinarily, an approvable drug becomes fully approved within days to weeks.

Drugs marked (D) are those cited as important by deHaen*; (W) indicates FDA interpretation that Wardell* considered the drug to be potentially important medically. Absence of either mark does not itself imply lack of medical importance because deHaen used various criteria and dealt mainly with drugs in England, France, Germany, Italy, Japan and Switzerland; Wardell's data concerned Britain and his evaluations were largely confined to drugs in specific therapeutic categories, including cardiovascular, diuretic, respiratory, anti-infective, anticancer, centrally-acting, anesthetic, analgesic, and gastro-intestinal drugs.

*REFERENCES

F.D.C. Reports, April 1, 1974 from a tabulation prepared under a special arrangement with Paul deHaen. Includes material from deHaen's "New Product Survey" and "Watchlist" of 50 promising products in U.S. pharmaceutical R & D.

Wardell, W.M.: Introduction of new therapeutic drugs in the United States and Great Britain: An international Comparison, Clinical Pharmacology and Therapeutics, pp 773-790, Sept-Oct. 1973.

Wardell, W.M.: Developments since 1971 in the patterns of introduction of new therapeutic drugs in the United States and Britain. Presented at the American Enterprise Institute in Washington, D.C. on July 26, 1974.

IND SUBMITTED IN U.S.

ALBUTEROL (Salbutamol) (W,D) This bronchodilator drug is currently being investigated under two INDs: one for an aerosol form submitted in 1969 and one for an oral dosage form submitted in 1970. Because of problems with the metered dose delivery systems studies of the aerosol were curtailed in 1972, and an NDA submitted (in 1973) for this form was withdrawn in 1974. Studies of the aerosol are currently underway employing a new delivery system, and studies of the oral dosage form continue. Similar adrenergic stimulant bronchodilators are available, including metaproterenol and isoproterenol, though albuterol is claimed to be more bronchoselective and to have lesser cardiovascular side-effects than isoproterenol.

ALCOFENAC An IND was originally submitted in 1970 for this drug as "mervan"; the name was changed to alclofenac in 1971. The drug was investigated as an alalgesic in the treatment of rheumatoid arthritis. It was found to produce gastrointestinal side-effects and not to be as effective as aspirin. The sponsor voluntarily discontinued the investigations in 1972. Suitable alternative drugs include aspirin, indomethacin and a number of non-hormonal analgesic/anti-inflammatory drugs either approved or under study.

ALPRENOLOL (W,D) INDs were submitted for this beta adrenergic blocking agent in 1966 and 1971 for its use as an anti-arrhythmic agent and for the treatment of angina pectoris. Carcinogenic studies in animals revealed an increase in numbers of tumors at higher doses; however, fewer were found in a second study. Clinical studies were withheld in 1971 pending resolution of animal toxicity problems which were common, at that point, to beta blockers. This drug was voluntarily discontinued in 1973 by the firm, the reason given being other research commitments. Propranolol is the marketed product available in this pharmacological class. Alprenolol appears to resemble oxprenolol, which is also under study and is described in more detail below.

AMILORIDE HCL (W) This is a potent potassium-sparing diuretic agent for which a commercial IND was filed in 1964. This drug was for use as a diuretic in patients who were unable to conserve potassium. An NDA was subsequently submitted in 1968 and found later that year to be not approvable. The studies were based on an inappropriate patient population, and there were some deaths. Not all of the latter were attributed to the drug directly, but fifteen were attributable to hyperkalemia. At the present time there are no studies ongoing with this product. Acceptable alternatives in this potassium-sparing diuretic class are marketed in the U.S.; e.g., triamterene and spironolactone.

AMOXICILLIN (D) Fully approved NDA (1974) Amoxil (Beecham); Larocin (Hoffman-LaRoche) - antibiotic for treatment of infections due to susceptible strains of Gram-negative and Gram-positive organisms.

ASPARAGINASE (D) This is a cancer chemotherapeutic agent for use in acute lymphocytic leukemias. Two INDs were submitted in 1966. Studies have shown the drug to have some effectiveness in producing remissions, but early high hopes have not been fully borne out. The drug is very expensive to produce and there are other agents available which also produce remissions. The INDs are still active, but there is a paucity of ongoing study by the investigators. Other suitable alternatives for acute lymphocytic leukemia presently on the market are vincristine sulfate - approved (1963); prednisone (1953); methotrexate (1955); cyclophosphamide (1959) and 6-thioguanine (1966).

BACLOFEN (D) This drug is proposed as a skeletal muscle relaxant. It is a derivative of gamma amino butyric acid (GABA) and is unrelated to other muscle relaxants, so it is of considerable pharmacological interest. The sponsor submitted an IND in 1969. Clinical trials are underway to test its ability to reduce muscle hypertonicity and for the treatment of dyskinesias, but the sponsor has not been pursuing investigational development of this drug with any degree of rapidity. Satisfactory additional drugs, such as diazepam and dantrolene, are marketed in the U.S. for similar uses; no advantages of baclofen are yet evident, but since therapies of spasticity and dyskinesia are generally unsatisfactory there would be marked value in a new and more effective drug.

BECLOMETHASONE PROPIONATE (W,D) This is a corticosteroid proposed for use in bronchial asthma and administered by inhalation. An IND was submitted in 1973, and an NDA in 1974. Additional data for the new drug application were submitted later in 1974 and the application is still under review. The potential advantages of this product are that it may provide the effectiveness of oral corticosteroids without the same adverse effects on the hypothalamic-pituitary-adrenal axis (HPA axis), or it may permit a decrease in the concomitant dose of oral corticosteroids. Dexamethasone for bronchial asthma by inhalation is currently marketed in the U.S., but may depress the patients' HPA axis. Thus, this development could represent a modest advance for some patients.

BENAPRYZINE This is an anticholinergic/antiparkinson agent chemically and pharmacologically similar to trihexphenidyl. An IND was submitted in 1970 and clinical studies are in progress, with no NDA as yet having been submitted. Marketed drugs of this class include trihexphenidyl and benztropine, which are used alone or with L-Dopa for the treatment of Parkinson's disease. A potential advantage of this drug lies in claims of fewer peripheral and central nervous system adverse effects, such as confusion and hallucinations.

BENORYLATE This analgesic/anti-inflammatory drug, for which INDs have been submitted by sponsors in 1968 and 1973, contains an ester of sodium salicylate and acetaminophen. Clinical studies for use as an analgesic and for rheumatoid arthritis are in progress. This particular formulation is not available on the U.S. market, but the basic chemical entities are marketed, along with a wide variety of analgesics and satisfactory anti-inflammatory agents.

BENZOCTAMINE (D) This drug is a tricyclic drug used as a minor tranquilizer, for which the sponsor submitted an IND in 1967. It was discontinued in 1974 due to lack of commercial interest and other research priorities, according to the sponsor. Controlled trials have shown little or no therapeutically useful effect. Numerous, apparently more effective drugs are marketed in the U.S. for anti-anxiety use.

BENZPERIDOL (D) This butyrophenone drug was proposed for treatment of anxiety and hypertension in an IND submitted in 1963. The sponsor discontinued this IND in 1964, reporting that it was because of increased commitments to other drugs. This drug is structurally very similar to droperidol and haloperidol which are marketed by the same sponsor for use, respectively, as a pre-operative tranquilizer (anti-anxiety) and an anti-psychotic agent. Butyrophenones as a class have a considerable potential for adverse effects, especially extrapyramidal symptoms, and there are a variety of drug classes other than butyrophenones which are on the market in the U.S. for adequate treatment of anxiety and of hypertension.

BETHANIDINE SULFATE (W D) This is an antihypertensive drug for which an IND was filed in 1964, and an NDA in 1966. The latter was deemed non-approvable in 1968, following several amendments which failed to provide evidence in well controlled trials of long-term safety and effectiveness. Another firm submitted an IND in 1971 and is presently performing animal studies and controlled clinical trials. Guanethidine is available in the U.S. as an adequate therapeutic alternative, although bethanidine is claimed to be somewhat easier to control and to have less tendency to produce diarrhea as a side effect.

BRETYLIUM TOSYLATE (D) In August of 1966 an individual investigator filed an IND to study its antiarrhythmic properties. A commercial IND was filed in 1968. Because of the drug's usefulness in recalcitrant and recurrent ventricular tachycardias and other dysrythmias, the Cardiovascular Advisory Committee reviewed the data and that of the literature in September of 1973 and found the data adequate to support this limited use. An NDA was filed by the firm in 1974 and is currently under review. There are acceptable alternative drugs for the treatment of arrhythmias, such as quinidine, procainamide, and lidocaine; as well as electrical conversion therapy. However, this drug might offer usefulness in patients who are unresponsive to these measures.

BROMHEXIN (Bisolvon) (W) For this mucolytic agent an IND was submitted in 1965, but discontinued in 1971 because of the sponsor's "re-evaluation of priorities." Acetylcysteine is available in the U.S. as a therapeutic alternative.

BUFEXAMAC (D) This is a non-hormonal anti-inflammatory agent for which the sponsor submitted an IND in 1970 to study the effect of the drug when applied as a topical cream to patients with atopic or eczematous dermatitis. In foreign studies the drug was administered orally to patients with arthritic conditions. Subjective improvement was reported but objective improvement was not substantiated. The sponsor discontinued the IND in 1972 because of lack of commercial interest. Topical steroid preparations are marketed in the U.S. for skin diseases and other non-hormonal anti-inflammatory agents are marketed or under study for systemic use in arthritic conditions.

BUFORMIN (D) This is an oral hypoglycemic agent of the biguanide class that is very similar to phenformin, another member of this class. A firm submitted an IND for buformin in 1969, but relatively little clinical research has been conducted under this IND, apparently because the drug seems to offer no significant advantage over phenformin, and because the same firm already markets phenformin in this country.

BUMETANIDE (D) This is a potent diuretic agent for which an IND to study its oral dosage form was submitted in 1972 and an application to study its IV form was submitted in 1974. The initial animal studies with the oral compound revealed dose-related renal toxicity; however, there was question as to whether or not the effect seen with the low dose employed was an exaggerated diuretic effect. Clinical studies with the oral form presently are underway with careful monitoring of benefit/risk parameters. The IV form has been held in abeyance because the application lacked subchronic toxicity studies in animals. These studies have recently been submitted and are currently under review. There are acceptable potent alternative diuretics marketed in the U.S.; e.g., furosemide and ethacrynic acid.

BUPIVICAINE (W) Fully approved NDA (1973) Marcaine (Winthrop) - local anesthetic.

CALCITONIN (salmon) This is a polypeptide hormone similar to porcine calcitonin, which is marketed in Europe. It has been evaluated for treatment of Paget's disease of bone, a condition for which there is no marketed effective therapy. An NDA was submitted in 1973. Additional significant data became available later that year, requiring additional evaluation. The NDA has recently been declared approvable and marketing in the U.S. is anticipated this Fall.

CARBIDOPA This is a decarboxylase inhibitor proposed for use in association with L-dopa in the treatment of Parkinsonism. An IND was submitted in 1970. Extensive clinical trials have been carried out in the United States and abroad. An NDA was submitted in late 1973 for the use of this drug in a fixed combination with L-dopa; a final decision on the application is imminent. Carbidopa is of clinical and pharmacological interest by virtue of its action in decreasing by 50 to 80% the amount of L-dopa required to treat Parkinsonian patients. It appears to permit better therapy in some patients than can be achieved with L-dopa alone by reducing certain adverse effects.

CARBENOXOLONE SODIUM (W) This product, which is synthesized from one of the components of licorice root, was introduced in the United Kingdom in 1962 as a treatment of peptic ulcer. Two INDs were submitted: one in 1965 for study of its effectiveness in the healing of gastric ulcer, and another in 1972 for study of its effect on the healing of duodenal ulcer. Theories of the mechanism include stimulation of mucus secretion, inhibition of pepsin, prolongation of the life of epithelial cells and protection against the noxious effect of bile upon gastric mucosa. The claimed effect of carbenoxolone in accelerating ulcer healing would represent a distinct advance, but requires substantiation. Also needed is further characterization of adverse reactions, especially fluid retention with edema and hypertension. In the meantime, conventional ulcer therapy usually provides a satisfactory alternative, with infrequent side effects.

S-CARBOXYMETHYLCYSTEINE (D) An IND was submitted in 1965 for evaluation of oral and nasal dosage forms of this decongestant. The IND was discontinued by the sponsor the same year because "the preliminary clinical evaluations did not offer sufficient promise to pursue these evaluations." Numerous decongestants are available for both oral and nasal use.

CEPHACETRILE SODIUM (D) Fully approved NDA (1974) Celospor (Ciba-Geigy) antibiotic of the cephalosporin class for treatment of the following infections when caused by susceptible micro-organisms: respiratory tract, skin and soft tissue, and urinary tract.

CEPHRADINE (D) Fully approved NDA (1974) Velosef (Squibb) antibiotic of the cephalosporin class for treatment of the following infections when caused by susceptible micro-organisms: respiratory tract, otitis media, skin and soft tissue, and urinary tract.

CHLORMETHIAZOLE (Heminevrin) This drug is a derivative of the thiazole moiety of thiamine (Vitamin B1); it has sedative-hypnotic and anticonvulsant properties and is proposed mainly for the treatment of alcohol-withdrawal syndrome. An IND was submitted in 1969. One clinical study was completed in 1970; since then, no further studies have been started. Other drugs such as Librium and Valium are marketed in the U.S. as adjuncts for treatment of the alcohol-withdrawal syndrome. The limited data available are not adequate to define the toxicity or relative efficacy of chlormethiazole.

CINNARIZINE This is a drug with purported antihistaminic, antivertigo, antiemetic and vasodilatory actions. It is chemically and pharmacologically a congener of cyclizine, meclizine, hydroxyzine, and other marketed antiemetic or tranquilizing drugs. Several INDs have been submitted by different commercial sponsors for this drug in 1963, 1967, and 1972; one was discontinued by the sponsor in 1965. Clinical investigations under the other INDs are currently in progress for use of the drug in vertigo and in vascular insufficiency, including cerebrovascular insufficiency of the aged. An NDA was submitted and approved in 1960 for use of the drug as an antihistaminic agent for allergic disorders and vertigo; however, the approval was withdrawn in 1971 because of failure of the applicant to submit required annual reports. As therapeutic alternatives, closely related drugs are available on the U.S. market for use as antiemetics or antivertigo agents, and no potential advantage is apparent for cinnarizine for these uses. A truly effective drug for vascular insufficiency would present a therapeutic advantage; but evidence that cinnarizine is such a drug is not available.

CLEMASTINE FUMARATE (D) An IND for this antihistamine was first submitted in 1966. An NDA was submitted in 1968, but was found non-approvable because of insufficient data from controlled clinical studies to support efficacy. Such data have not subsequently been submitted. Numerous other antihistamines are available.

CLOCORTOLONE PRIVALATE (D) An IND for this topical steroid was first filed in 1970 and was discontinued in 1971 for "lack of commercial interest." Another sponsor submitted an IND in 1973 and this application remains active. There are numerous topical steroids approved for the same indications, and no important advantages are yet apparent for this drug.

CLOFAZIMINE This antimicrobial is also known as amino-phenazine or lamprene. INDs were filed in 1963, 1966, 1967 and 1970 by government institutions and individual investigators to study the drug for the treatment of leprosy and tuberculosis. Some of the INDs were discontinued when the sponsors' studies were completed. Other INDs are still active and a limited number of leprosy patients continue to be treated as needed. No NDA has been submitted and none is anticipated. Because of the limited extent of use of the drug, it is supplied by the sponsors on a service basis. An alternate treatment for leprosy is dapsone, which is approved. There are several approved drugs for the treatment of tuberculosis.

CLOMIPRAMINE (D) Clomipramine is an antidepressant agent of the tricyclic drug class, for which the sponsor submitted an IND in 1969. In studies conducted to date the drug does not appear to have advantages over similar drugs with the same pharmacological activity. Side-effects and adverse reactions are similar to those produced by imipramine and amitriptyline, which are similar marketed tricyclic antidepressants.

CLONAZEPAM (D) This benzodiazepine derivative has been studied for potential anti-anxiety, muscle relaxant and anticonvulsant usefulness under an IND filed by the sponsor in 1963. Preclinical data indicated that it was markedly more potent than its congeners in antagonizing experimentally induced convulsions. Clinical trials proved that the agent is useful in the treatment of several types of epilepsy occurring in children. An NDA submitted in 1973 for the anticonvulsant indication in the treatment of petit mal, petit mal variant, myoclonic, akinetic and minor motor seizures has been reviewed and is approvable. Final approval depends upon labeling revisions and a decision from the Drug Enforcement Administration regarding its scheduling under the Controlled Substances Act. A similar drug marketed for this indication in the U.S. is diazepam (Valium). There will be a therapeutic gain in having an additional drug of this type for epileptic patients who may not respond to other available medications; in addition, clonazepam has been more thoroughly evaluated than diazepam or other benzodiazepines in certain seizures disorders. See also information on nitrazepam.

CLONIDINE (W,D) Fully approved NDA (1974) Catapres (Boehringer-Ingelheim) antihypertensive.

CLOPAMIDE This is a diuretic agent which has been studied under INDs filed in 1963 and 1968 for the study of Clopamide singly in the treatment of hypertension or combined with other antihypertensive agents. Clinical studies ongoing are limited in nature and would currently be considered to be in Phase II. There are acceptable alternative diuretics available (e.g., thiazide diuretics) and this drug appears to offer no significant advantages.

CLOTRIMAZOLE (D) This antifungal drug for topical and vaginal use was first submitted as an IND in 1970. An NDA for the topical cream was submitted in 1974 and is still under active review. Submission of an NDA for the oral form has been delayed by the finding of adrenohypertrophic effects in animals, of uncertain relevance to human toxicity. Available drugs approved for these indications are tolnaftate, haloprogin and griseofulvin.

CLOZAPINE (D) This is a phenothiazine-like drug used as an anti-psychotic. INDs were submitted by a commercial sponsor and an individual investigator in 1969, 1971 and 1973. The drug is being studied as an anti-psychotic agent and also is being used, at relatively low doses, for sociopathic behavior. There are alternative drugs marketed in the U.S. as anti-psychotics, such as the phenothiazine tranquilizers. Clozapine may have some advantage in that no extrapyramidal symptoms have been found thusfar in early tests.

COTRIMOXAZOLE See trimethoprim-sulfamethoxazole

CYCLACILLIN (D) The initial IND for this antibiotic was submitted in 1967. There are currently four active INDs, all in Phase III. The only problem associated with this drug has been the formation of crystals in urine of mice and rats. No correlation to humans has been noted. The drug is similar to ampicillin and amoxicillin, both of which are approved.

CYCLOPENTHIAZIDE This is a diuretic agent. An NDA was originally filed in 1961. Following the Kefauver-Harris Amendment of 1962 the firm submitted an IND in 1963. The NDA was eventually found non-approvable on the basis of inadequate preclinical as well as clinical evidence of safety and efficacy in 1968, although additional data were supplied during the intervening years. The IND was discontinued in 1971 by the sponsor. There are acceptable alternative diuretic agents available; e.g., thiazides and potassium-sparing diuretics.

CYPROTERONE ACETATE (D) This is a potent progestational agent of potential significance being investigated for various indications including benign prostatic hypertrophy, sexual hyperactivity, sexual deviance, and central nervous system effects. INDs were submitted by five sponsors during 1968, 1973, and 1974. Clinical trials are currently in progress in phases I and II, with the major research being conducted by individual investigators under research INDs. An Alternative progestin available in the U.S.for the endocrinologic indications is medroxyprogesterone acetate. This drug has been used abroad as an anti-androgen for sexual offenders. Two INDs for this use were submitted by individual research investigators in 1973. A drug useful in the treatment of sexual criminals would be an important therapeutic advance, but major questions of safety and efficacy for this use remain to be clarified.

DAUNOMYCIN This is an antineoplastic antibiotic closely related chemically and in antineoplastic activity to adriamycin. Two INDs were submitted in 1965, and an NDA in 1974. The latter application is currently under review and a regulatory decision regarding its approvability is expected soon. A therapeutic alternative is adriamycin, which was approved in August, 1974, as an antineoplastic for a wide range of solid tumors and leukemias.

DEBRISOQUIN SULFATE (W,D) This is an antihypertensive agent for which an IND was filed initially in 1963, with a subsequent NDA being filed in 1964. This NDA was declared non-approvable in 1969 because the studies were judged to be of poor design and of insufficient quality to document safety and effectiveness. The IND was discontinued by the sponsor in 1969. The drug is an adrenergic neuronal blocking drug similar in action to guanethidine, an antihypertensive drug which is marketed in the U.S.

DEPAKINE (Dipropylacetic acid) (D) This drug is an anticonvulsant of considerable pharmacological interest because of its chemical simplicity and because it is unrelated to available anticonvulsants. A research investigator, in 1974, submitted an IND for its use in various neurological conditions. In addition, FDA staff have discussed European data on use of the drug as a new anticonvulsant with a potential commercial sponsor, and a commercial IND submission appears imminent.
Dipropylacetic acid is presently in wide use in Europe for generalized seizures of both the tonic-clonic and absence types. Foreign experience suggests that adverse reactions present a lesser problem than with other anticonvulsants and that patients refractory to other drugs sometimes can be controlled with dipropylacetic acid. For these reasons, this drug may offer advantages in the treatment of some epileptics. Alternative therapy is available, however, for all of its known potential uses.

DIBENZEPINE This is a tricyclic antidepressant drug for which the sponsor submitted an IND in 1966. The IND was discontinued by the sponsor in 1973. Similar drugs are marketed in the U.S. for this indication, such as imipramine and amitriptyline. It has been suggested that Dibenzepine may have a slight advantage over other tricyclic antidepressants, specifically in decreased severity of certain side effects. It does not appear, however, to represent a marked therapeutic advance.

DISOPYRAMIDE (D) This is an anti-arrhythmic agent for which an IND was initially filed in 1965 to study the oral form of the drug. An IND was subsequently filed in March of 1974 to study the intravenous form. An NDA filed in 1970 was withdrawn in 1971, subsequently refiled in 1973, and deemed not approvable in 1974 because of inadequate clinical studies to document safety and effectiveness. There are acceptable alternative drugs for the treatment of arrhythmias; e.g., lidocaine, quinidine, and procainamide.

DOXORUBICIN Fully approved NDA (1974) Cerubidine (IVES)-antineoplastic

EPICILLIN (D) The initial IND for this antibiotic was submitted in 1969 and the drug is currently undergoing clinical trials. The drug is similar to ampicillin and amoxicillin, both of which are approved.

ETOGLUCIDE This is an alkylating agent also known as epodyl for the treatment of various types of neoplasms. An IND was filed in 1965 and then discontinued by the sponsor in 1967. There are several alkylating agents presently marketed in the U.S., such as chlorambucil - approved (1957); cyclophosphamide (1959); nitrogen mustard (1950); phenylalanine mustard (1964) and triethylemelamine (1953). These drugs are used primarily for the treatment of Hodgkin's disease, lymphosarcomas, chronic leukemias, and breast and ovarian cancers.

FENCAMFAMINE This is a CNS stimulant, related to amphetamines, for which NDAs were submitted in 1967, 1970, and 1972 for the treatment of mild depression. These applications were subsequently withdrawn by the sponsor in 1972, due to the fact that the clinical trials did not demonstrate efficacy, and there are no ongoing studies presently. Other drugs are marketed in the U.S. for this indication, such as imipramine and amitriptyline. The use of amphetamines and related drugs in depression is considered inadvisable by many clinicians because of the potential of these drugs to produce dependence and tolerance. This would represent a potential therapeutic disadvantage of fencamfamine compared with available alternative antidepressants of the non-amphetamine type.

FENFLURAMINE (W,D) Fully approved NDA (1973) Pondimin (Robins) - An appetite suppressant chemically closely related to amphetamines, possessing less adverse stimulant effects, but with a potential for producing depression.

FENOPROFEN This is a non-hormonal anti-inflammatory agent for which analgesic and antipyretic properties are also claimed. INDs were submitted in 1969 for studies in rheumatoid arthritis and in 1971 to study the analgesic and antipyretic properties. An NDA was submitted in 1974 and is currently under review. Fenoprofen is one of several non-hormonal anti-inflammatory drugs currently under investigation and review. The anti-inflammatory activity of Fenoprofen appears to be comparable to that of aspirin and other non-hormonal anti-inflammatory agents already marketed in the U.S. It is claimed that there are fewer gastrointestinal side effects and tinnitus with fenoprofen than aspirin; data in support of these claims are currently under review.

FLUCLOXACILLIN (D) An IND for this antibiotic was submitted in 1970, and clinical evaluation is in progress. This drug is similar to oxacillin, cloxacillin, and dicloxacillin, all of which are approved.

FLUFENAMIC ACID This anti-inflammatory anthranilic acid derivative was studied under an IND submitted in 1963. Studies were discontinued in 1972 because the sponsor found that a related drug, sodium meclofenamate, promised superior anti-inflammatory activity. No further trials have been undertaken. The drug has no known advantages over such alternatives as aspirin and indomethacin, or a number of non-hormonal anti-inflammatory drugs presently under investigation.

FLUPENTHIXOL (D) This drug is a thioxanthene derivative, related to the major antipsychotic tranquilizers, which is proposed for study as an antidepressant. The sponsor submitted an IND in 1973, and clinical study is still in an early phase. The chemically related neuroleptics, thiothixene and chlorprothixene, are available in this country for use in psychoses; available alternative anti-depressants include imipramine and amitriptyline.

FLUPHENAZINE DECANOATE (D) Fully approved NDA (1972). Prolixin decanoate (Squibb) - management of manifestations of schizophrenia. Claims that this ester of fluphenazine is longer acting than the other, earlier ester, the enanthate, were not considered adequately demonstrated, and have not been permitted in labeling and promotion of this drug.

FLUSPIRILENE (D) This drug is a long-acting antipsychotic, a butyrophenone, chemically and pharmacologically related to haloperidol. A sponsor submitted an IND in 1970 for maintenance therapy in chronic schizophrenics, and clinical trials are currently in progress. Other drugs are marketed in the U.S. for this indication, such as the phenothiazines and haloperidol. Potential advantages of this drug are the weekly dosage schedule and the reported selective effect on the delusional component of schizophrenia.

FONAZINE MESYLATE (D) An IND for this analgesic/antihistaminic drug was first submitted in 1965. A major problem with this drug was that chronic toxicity studies in animals showed kidney and liver pathology. Because of these preclinical findings, human investigations proceeded cautiously. FDA requested that patients under study be closely followed. The IND was discontinued by the sponsor in 1974, because of a lack of current interest in marketing this product. Satisfactory therapeutic alternatives are available including cyproheptadine, promethazine, and methysergide.

FUSIDATE SODIUM (W,D) An IND for this antibiotic was first submitted in 1963, and was discontinued in 1971. A second IND for a different dosage form was submitted in 1966 and was discontinued in 1968. An NDA was submitted in 1968 and was found not approvable in 1971 because of inadequacies in studies of blood levels and excretion of the drug, as well as a lack of controlled clinical evaluations. There has been no further study. Approved antibiotics with similar spectra are cloxacillin and dicloxacillin.

GESTONORONE CAPROATE (D) This is a progestational agent for which an IND was submitted in 1965 for the treatment of benign prostatic hypertrophy. This investigation was discontinued by the sponsor for the stated reason of lack of commercial interest. There is no known effective drug therapy for benign prostatic hypertrophy.

GLIDIAZINE (D) An IND for this sulfonylurea-type oral hypoglycemic agent was submitted in 1971. The investigations are in Phase II. The drug is currently being compared against products of the same type which are commercially available. There is no apparent significant advantage of this drug over those currently available, nor is there any evidence to suggest that this drug may be safer than tolbutamide in terms of cardiovascular risk.

GLYBURIDE (D) This is an oral hypoglycemic agent of the sulfonylurea class that is more potent than other commercially available agents of this class. NDAs were submitted by two firms in mid and late 1973. Although the initial evaluation of these NDAs by FDA was favorable based on the clinical testing in this country, FDA has recently received information that a significant number of deaths from hypoglycemic reactions have occurred with the use of this agent in other countries where the drug is marketed. FDA is currently investigating these reports further, and a final regulatory decision is awaiting resolution of this problem and resolution of the general problem of a warning for all oral hypoglycemic drugs in regard to possible excess cardiovascular mortality (UGDP study).

GUANOXAN SULFATE INDs for this antihypertensive agent were originally filed in 1965 and 1967 for use of the drug singly and in combination with a diuretic. They were discontinued in 1967 because of clinical evidence of jaundice in 1% of patients and laboratory evidence of abnormal liver function in 10 to 20% of cases. The acceptable alternative therapy is quanethidine, which is marketed in the U.S.

IBUPROFEN (D) Fully approved NDA (1974) Motrin (Upjohn) non-hormonal anti-inflammatory agent.

IPRINDOLE This is a tricyclic indole anti-depressant and tranquilizer for which an IND was submitted in 1963 and an NDA in 1970. When the data were found inadequate to support claims of safety and effectiveness in depressed patients, no additional clinical studies were undertaken. There are presently related antidepressants on the market in this country, such as imipramine and amitriptyline and a variety of tranquilizers. No advantages have been demonstrated for iprindole over these drugs in either depression or anxiety.

ISOETHARINE (W) This beta-agonist bronchodilator, under an NDA approved in 1961, was marketed in the U.S. in combination with the alpha-agonist, phenylephrine, or the antihistamine, thenyldiamine, as bronkometer and Bronkosol (Breon), respectively. Pursuant to the NAS/NRC review, thenyldiamine was deleted from the formula and the product is now marketed as combinations of isoetharine methanesulfonate or hydrochloride and phenylephrine hydrochloride (Bronkometer-2, Bronkosol-2). Isoetharine has not been marketed in the U.S. as a separate substance or in an oral dosage form, but has been investigated under a number of INDs. INDs were submitted for the methanesulfonate as an aerosol, tablet, syrup, and controlled release tablet between 1963 and 1967, and all were discontinued by 1970 because the studies were completed. (the aerosol IND was reinstated in 1974 to allow for an emergency shipment). The hydrochloride has been investigated under two INDs; one for an intravenous infusion (submitted in 1964) was delayed pending additional animal safety studies which have been completed, and studies under an IND (submitted in 1973) for a sustained release tablet are currently proceeding. No NDA has yet been submitted. The relative bronchoselectivity of isoetharine is shared by such other beta-agonists as metaproterenol, terbutaline (both recently approved) and albuterol (under study); isoproterenol is also a therapeutic alternative.

LACTULOSE This drug, for which an IND was initially filed in 1971, is being investigated for its use in portal systemic encephalopathy. Its postulated mechanisms include (a) inhibition of proteolytic bacteria in the gut, (b) inhibition of absorption of nitrogenous metabolites of bacteria or (c) alteration of absorptive function of the gut mucosa. Studies are in progress and data are being collected under a common protocol. The drug appears to be clinically effective in some patients with hepatic encephalopathy, and few adverse effects have been noted as yet. It appears to have no advantage over neomycin in the management of acute hepatic coma, but may represent a potential contribution in the treatment of chronic encephalopathy in patients with severe liver disease.

LORAZEPAM (D) For this anti-anxiety agent of the benzodiazepine group, the sponsor submitted an IND in 1965. Although no significant problems have become apparent with this particular drug, clinical trials have not progressed rapidly. The IND now is in the late stages of investigation and appears to be focusing on anxiety associated with certain specific states. Adequate alternative drugs marketed in the U.S. for these indications include diazepam, chlordiazepoxide and oxazepam. No therapeutic advantages of lorazepam over these drugs seem apparent.

MAPROTILINE (D) This is a tricyclic antidepressant for which an IND was submitted in 1969. An NDA was submitted by the sponsor in late 1973, but due to a lack of adequate and well-controlled clinical trials, it was declared non-approvable in 1974. Satisfactory drugs are marketed in the U.S. for this indication, such as other tricyclic antidepressants, (e.g., imipramine, amitryptiline and nortriptyline). There are no apparent potential advantages of this product over marketed drugs.

MEBEVERINE An IND for this antispasmodic was submitted in 1967 and studies were conducted in patients with irritable bowel syndrome. The sponsor discontinued the IND in 1969 when foreign trials revealed that the proposed dose caused alterations in heart rate, dizziness, tremors, nausea and vomiting in approximately 75% of patients. Alternative antispasmodics available for this indication include belladonna alkaloids and their derivatives as well as many synthetic compounds.

MEDAZEPAM (D) This drug is a benzodiazepine derivative for which a sponsor submitted INDs in 1963 and 1965 for its study as an anti-anxiety agent. The sponsor submitted an NDA in 1969, with several resubmissions having been made subsequently. Non-approvable letters on this NDA were issued in 1970, 1971 and 1972. In all of the submissions thusfar, there has been a lack of substantial evidence of efficacy. Other drugs of the same class, such as chlordiazepoxide and diazepam, are marketed in the U.S. for this indication by the same manufacturer. No potential advantages of medazepam over these other benzodiazepines are thusfar apparent.

MEFRUSIDE An IND was submitted in 1967 for this oral diuretic compound, which animal studies suggested has a potency in the range of that seen with ethacrynic acid and furosimide but with a slower onset of action and a longer duration of effect. The firm stated in 1972 that there were no clinical investigations underway, and this apparently remains the current status of the drug. There are satisfactory alternatives in ethacrynic acid and furosimide.

MESNA (D) This mucolytic agent was investigated under an IND submitted in 1971. The IND was discontinued in 1974 for the reason that "the estimated commitment of resources required to meet regulatory requirements for clearance of this NDA is such that continued development of this product is not justified at this time." Acetylcysteine is available in the U.S. as a therapeutic alternative.

METAPROTERENOL (W) Fully approved NDA (1973) Alupent (Boeringer-Ingelheim) bronchodilator.

METHISAZONE An IND for this antiviral drug was submitted in 1963. Data shows that there is a potential for hepatotoxicity and its use is limited to patients with serious problems of vaccinia. No NDA has yet been submitted. There are no drugs presently approved for conditions which would be treated by methisazone, and so the drug potentially offers a significant advantage in situations in which the seriousness of the infection warrants the toxic risk.

METHYLCYSTEINE (D) INDs for this mucolytic agent were submitted by two firms in 1964 and 1965. Both were discontinued in 1965, one for reported lack of marketing interest and the other because preliminary clinical evaluations did not suggest sufficient promise. This drug is not currently being investigated in the United States. Acetylcysteine, a simialr mucolytic drug; is marketed in this country.

METHYLDIGOXIN (D) This is a cardiac glycoside (digitalis-like drug) for which an IND was filed in 1972. The investigation under this application was discontinued in 1974 by the sponsor who gave as a reason that the drug did not appear to be significantly different from its chemical congener,digoxin. Digoxin, digitoxin, and other cardiac glycosides are all available in the U.S.

METOCLOPRAMIDE (W,D) This drug is a centrally-acting antiemetic which is also purported to have a direct stimulating effect on gastrointestinal smooth muscle. An IND submitted in 1964 for its antimetic effect was discontinued in 1968 for lack of interest in this country, according to the sponsor. A second sponsor submitted INDs in 1971 and 1973. An NDA for use as a gastrointestinal stimulant was found to be incomplete in 1974 for lack of adequate evidence of safety and effectiveness. It is chemically different from marketed antiemetics of the diphenylpiperazine (e.g., cyclizine) or phenothiazine (e.g., prochlorperazine) type and so has been claimed to possess therapeutic advantages, such as less adverse effects over these available alternative antiemetics, but trials to date have not established effectiveness.

METOLAZONE Fully approved NDA (1973) Zaroxolyn (Pennwalt) - diuretic and antihypertensive.

NAFOXIDINE This is an oral anti-tumor and anti-estrogen agent. INDs were submitted in 1965 for study of anti-fertility properties and use as an anti-tumor agent for breast cancer, but were discontinued in 1966 and 1967 because of the production of lens opacities in animals. An IND was reinstated in 1969 and the drug is currently being evaluated for the treatment of renal carcinoma and advanced breast cancer. No NDA has yet been submitted. If this drug proves to be effective, it may offer advantages in some patients having these malignancies despite its potential toxicity.

NAPROXEN (D) This is a non-hormonal anti-inflammatory agent. INDs were submitted in 1968 for studies in rheumatoid arthritis and other arthritic conditions, in 1970 for study of analgesic properties, and in 1973 for study of antipyretic properties in children. An NDA was submitted in 1974 and is currently under review. Naproxen is one of several non-hormonal anti-inflammatory drugs currently under investigation and review. The anti-inflammatory activity of Naproxen appears to be comparable to that produced by aspirin and other non-hormonal anti-inflammatory agents already marketed in the U.S. It is claimed that patients who have undesirable gastrointestinal or central nervous system side effects while receiving aspirin may be able to tolerate Naproxen; data in support of this claim are currently under review.

NATAMYCIN (Pimaricin, Tennecetin). Several NDAs were approved in 1962 for this antibiotic under the name of tennecetin for use as an antifungal agent for vaginal candidiasis. It is not marketed, since the firm has never submitted the drug for certification. An IND was submitted for ophthalmic use in 1968 by an individual investigator. This IND is still active, but not enough data have been accumulated for submission of an NDA. There are no drugs which have been approved for antifungal therapy in ophthalmic use, and there is preliminary evidence that this drug may be useful for this purpose.

NICLOSAMIDE An IND for this anthelminthic was first submitted in 1966 and was discontinued in 1967 because of lack of investigators. Another IND for the same drug was submitted in 1968 by a different sponsor and is still active. No NDA has been submitted. Other drugs available for the same indications are dichlorophene and quinacrine hydrochloride. It is claimed that niclosamide offers a safety advantage since it is not absorbed from the gastrointestinal tract.

NIFURATEL This nitrofuran antimicrobial and trichomonacidal drug was studied under an IND submitted in 1968. The IND was discontinued in 1969 for lack of commercial interest. It was terminated in 1970, along with similar nitrofurans, because of the association of this class of drugs with tumorigenesis in animals. An approved drug for the trichomonas indication is metronidazole (Flagyl); effective drugs are available for the proposed antimicrobial uses.

NIRIDAZOLE An IND for this amebicide and schistosominthic was first submitted in 1966. The commercial sponsor has discontinued this IND because of lack of commercial interest in the United States. Other INDs are held by individual physicians, and are restricted to hospital patients with severe schistosomal problems. The restrictions are imposed because of possible adverse effects on heart, brain and blood. Other preparations available for treatment of these diseases are antimony potassium tartrate and antimony sodium thioglycollate. These latter drugs are much less expensive, but it is claimed that niridazole may be more effective.

NITRAZEPAM (W) This is a benzodiazepine derivative for which a commercial IND was submitted in 1963; trials were carried out for uses common to other benzodiazepines, but chiefly for use as an anticonvulsant or a hypnotic. Although trials continue on a limited basis, the sponsor has indicated that they are not developing the drug with a marketing interest at this time. Another benzodiazepine marketed in the United States by the same company, for many uses including use as as anticonvulsant, is diazepam. Another more closely related benzodiazepine of the same company, clonazepam is the subject of an NDA near approval for anticonvulsant use. Clonazepam and nitrazepam have appeared very similar in anticonvulsant usefulness, including use in myoclonic seizures, but there is clearly a possibility that any such drug may provide special advantages for certain refractory epileptics or certain special types of epilepsy; e.g., infantile spasms. See also information on clonazepam. A major use of nitrazepam overseas appears to be as a hypnotic. A very similar benzodiazepine, flurazepam, is available from the same manufacturers as an alternative hypnotic in the U.S.; no therapeutic advantages of nitrazepam over flurazepam are apparent.

OPIPRAMOL This drug is a tricyclic anti-depressant for which an IND was submitted by the sponsor in 1963. An NDA for this product was voluntarily withdrawn by the sponsor in 1964, and the IND was suspended on the grounds of hepatic and renal toxicity in animals and a claimed high incidence of adverse reactions in humans. Adequate and less toxic antidepressants are marketed in the U.S., including imipramine and amitriptyline.

OXPRENOLOL (W) This is a beta adrenergic blocking agent which is being studied for its cardiac antiarrhythmic as well as its antihypertensive properties. An investigational application was originally filed in 1969 by a firm licensed by the parent company. Animal studies, performed according to our guidelines for carcinogenic trials, have been completed and the drug has been cleared for clinical trials. An accepted and available beta blocking agent is propranolol, although oxprenolol is purported to exert less myocardial depression than propranolol.

OXYPERTINE (D) This is an anti-anxiety drug of the benzodiazepine type, for which an IND was submitted by the sponsor in 1968. The sponsor discontinued studies in 1971 and the stated reasons were lack of commercial interest. Similar drugs are marketed in the U.S. for this indication such as diazepam, oxazepam, and chlordiazepoxide.

OXYFEDRINE (D) An IND was originally filed in 1969 for study of this beta-adrenergic stimulator (vasodilator) in the management of coronary insufficiency, angina pectoris and myocardial infarction. The firm has since discontinued the IND because of lack of potential regarding effectiveness. Nitroglycerin is an accepted alternative therapy in angina pectoris.

PANCREOZYMIN This term refers to the pancreatic-enzyme stimulating action of cholecystokinin-pancreozymin (CCK-P2), a hormone formed in the upper intestinal mucosa which stimulates contraction of the gall bladder and secretion of enzymes by the pancreas. INDs have been filed for both the natural (cecekin) and synthetic (OP-CCK) products, and clinical trials are currently in progress to evaluate the applicability of the products as diagnostic aids in cholecystography, in collection of the contents of the gall bladder, and in disease of the pancreas. The products offer the possibility of improving the diagnosis of diseases of the gall bladder and pancreas.

PANCURONIUM BROMIDE Fully approved NDA (1972). Pavulon (Organon) Skeletal muscle relaxant.

PARKIN (D) This is a foreign brand name for profenamine or ethopropazine, a phenothiazine. An NDA for ethopropazine was fully approved in 1953 under the brand name Parisidol (Warner-Chilcott) for use in parkinsonism.

PEMOLINE (D) This is a CNS stimulant for which the sponsor first submitted an IND in late 1965. An NDA first submitted in 1968 for reversal of emotionally induced fatigue and mild depression was nonapprovable for lack of demonstrated efficacy and because of manufacturing deficiencies. The NDA was resubmitted in 1972 for treatment of hyperkinetic syndrome (MBD) in children. Initially found inadequate because of clinical trial deficiencies and insufficient longterm data, the NDA was supplemented to remedy these deficiencies, and an approvable letter issued in mid July, 1974 for this indication (Cylert, Abbott). Other drugs are marketed in the U.S. for similar indications, such as methylphenidate and the amphetamines. Although apparently no more effective than the latter drugs, pemoline may have an advantage in that a once-daily dosage is adequate, eliminating the need for children to receive medication at school, and the abuse potential appears somewhat less than with other stimulant drugs.

PENTAGASTRIN (W,D) Fully approved NDA (1974) Peptavlon (Ayerst) diagnostic agent for gastric secretion.

PIMOZIDE (D) This is an antipsychotic tranquilizer, related to butyrophenone, for which one commercial sponsor submitted an IND in 1968, and individual investigators submitted INDs in 1972 and 1973. An NDA was submitted in mid-1973, but was found non-approvable due to a lack of adequate and objective data. The FDA has been in contact with the sponsor in order to effect resolution of the problems of previous clinical trials. Other drugs such as the phenothiazines are marketed in the U.S. for these indications. The drug is of psychophamacological interest in that it appears to act exclusively upon dopaminergic pathways in the brain, although the clinical implications of this are not clear. There are claimed advantages with respect to decreased adverse effects, but trials to date have not substantiated this. It appears to have a clear-cut disadvantage compared with most other antipsychotics in that it cannot be used for acute therapy, but only in maintenance.

PINDOLOL This beta adrenergic blocking agent has been studied for cardiac antiarrhythmic properties under INDs filed in 1968 and 1969. The investigation to date is limited to 30-day, Phase II-type studies to document safety and efficacy. At present the firm is performing animal carcinogenicity studies as well as exploring other toxicity problems. An acceptable antiarrhythmic agent of the same pharmacologic class is propranolol. Pindolol appears to resemble oxprenolol, which is also under investigation and is described in more detail above.

PIRINITRAMIDE This drug is chemically related to methadone and, more distantly, to meperidine. It is a synthetic narcotic analgesic, said to be more potent than morphine. An IND for parenteral use was submitted in 1968 and discontinued by the sponsor in 1969 because the drug did not appear to have sufficient advantage over existing marketed products. The drug appears to offer no obvious advantage over morphine. It produces respiratory depression, nausea, and has a high physical dependence liability. There are satisfactory alternative agents presently available in the U.S. such as morphine, meperidine, or pentazocine.

PIVAMPICILLIN (D) An IND for this antibiotic was submitted in 1970 and was terminated in 1971 due to indications of hepatotoxicity. The same IND was reinstated in 1974 after the company had demonstrated satisfactorily that the hepatotoxicity was species-specific, appearing only in the dog. No clinical trials are currently in progress. This drug is similar in activity to ampicillin and amoxicillin, both of which are approved.

PRACTOLOL (W,D) This is a beta adrenergic blocking agent which is being studied as a cardiac antiarrhythmic drug. An IND was submitted by the sponsor in 1969. Animal studies, performed according to our guidelines for carcinogenic trials, have been completed and the drug has been cleared for clinical trials. An accepted and available beta blocking agent is propranolol, although practolol is purported to have greater cardioselectivity and to exert less myocardial depression then propranolol.

PRAZEPAM (D) This is an anti-anxiety drug, of the benzodiazepine type, for which the sponsor submitted an IND in late 1963. An NDA was submitted in late 1972 and declared non-approvable due to inadequacies in the clinical data. The NDA was recently resubmitted and is currently under active review. Other drugs marketed in the U.S. for these indications are chlordiazepoxide and oxazepam. No advantages over other benzodiazepines are apparent.

PRENYLAMINE This is a coronary vasodilator drug proposed for use in angina. An IND was submitted by the sponsor in 1963, and an NDA in 1963. The NDA was declared nonapprovable in 1969 because of insufficient manufacturing controls information, inadequate pharmacology data, and inadequate clinical documentation of effectiveness. Investigation was continued intermittently under the IND until 1972, when the IND was discontinued by the sponsor for the stated reason of insufficient marketing promise. Effective alternative drugs, such as nitroglycerin, for the treatment of angina are available on the market.

PROPRANIDID (W) This is an intravenous, nonbarbiturate anesthetic for which two INDs were submitted: one submitted by a commercial sponsor in 1963 was discontinued in 1964 because of lack of commercial interest; the other submitted by an investigator in 1966 was discontinued in 1968 without specified reasons. There presently is no evident continuing development of this drug in the U.S. It is more rapidly metabolized than thiopental, and therefore is claimed to be especially useful in brief outpatient procedures where early consciousness and lack of residual obtundation would be advantageous. There are a number of adverse reactions with this drug, but it is not clear whether these are more frequent than with alternative agents. Marketed therapeutic alternatives include thiopental and ketamine.

PROPERICIAZINE (periciazine) This drug is a cyano-substituted phenothiazine antipsychotic tranquilizer; the cyano group distinguishes it from otherwise similar drugs available for this indication (e.g., chlorpromazine, thioridiazine). An IND submitted by a commercial sponsor in 1964 was discontinued because of the drug's lack of advantage over available therapy. Moreover, a narrow margin of safety was suggested by the rat chronic toxicity study which showed rather severe, but inadequately characterized, hepatic and renal toxicity. Subsequently, there were INDs submitted in 1968 by two research investigators and one in 1972 by another commercial sponsor for investigation of this drug in limited patient populations with types of psychoses refractory to other treatment. These included seriously distressed adolescents, "head-bangers" and "self-mutilators", dangerous to themselves and others. The animal data submitted to the latter IND was that which had been submitted to the first commercial IND; and consequently, additional animal toxicity studies were requested by the FDA to better characterize the toxic potential of the drug. This latter commercial sponsor discontinued their IND in 1974 because of no further commercial interest. One research investigation was discontinued in 1972; the other is still in progress to a limited extent.

PROPIRAM FUMARATE (D) This is a drug in the potent analgesic category for which INDs were submitted in 1966. Early animal studies showed some toxicity problems which delayed clinical trials temporarily; these problems have since been resolved. Although clinical trials continue under these INDs, investigative development of this drug has not been rapidly pursued. There are acceptable alternative drugs marketed in the U.S. for this indication, such as morphine and meperidine. There are two potential advantages of this drug over morphine-like drugs: (1) It may have less potential for abuse, and (2) It is synthetic and does not require raw opium as a source for chemical synthesis.

QUINGESTANOL ACETATE (D) This is a progestational agent for which three INDs were submitted in 1965 and 1969. All of the INDs have been discontinued by the sponsor for lack of commercial interest and "noncompetitive efficacy." It was investigated for use as a microdose contraceptive agent but failed to meet acceptable standards of effectiveness. Norethindrone is an alternative progestational agent used as a contraceptive agent which is marketed in the United States.

RIFAMPIN Fully approved NDA (1971) Rifadin (Dow); and Rimactane (Ciba-Geigy) - an antibiotic for pulmonary tuberculosis and meningococcal carriers.

RIMITEROL (W) An IND was first submitted in 1971 for study of an aerosol of this bronchodilator of the beta-agonist type. The IND is active, but satisfactory study protocols have not yet been submitted. Satisfactory therapeutic alternatives include isoproterenol and metaproterenol, though rimiterol is said to have greater bronchoselectivity than does isoproterenol.

RITODRINE (D) This is a uterine muscle relaxant for which INDs were submitted in 1969 and 1971. One was discontinued by the sponsor following the completion of the planned studies in phases I and II. The active IND is in phase III, and is for studies of the drug's effectiveness in relieving premature labor, a condition for which there is no effective approved drug. The drug is structurally similar to isoxsuprine, a commercially marketed drug formerly labeled for this indication. The indication was deleted from its labeling pursuant to an efficacy review (DESI) conclusion that there is a lack of substantial evidence that the drug is effective for this indication.

SLOW RELEASE POTASSIUM SUPPLEMENTS (W) INDs for controlled-release potassium chloride tablets were submitted by two sponsors in 1971. Both of these sponsors now have NDA's before the Agency that are under active review. These tablets are composed of potassium chloride formulated in a wax-matrix core. Adverse reactions data from foreign marketing experience indicate that these wax-matrix tablets have much less potential for producing serious gastrointestinal lesions (e.g., perforation or obstruction of bowel) than conventional potassium chloride tablets or enteric coated tablets, although they are not risk-free in this regard. These tablets therefore offer a safety advantage over the currently marketed solid dosage forms of potassium chloride in the U.S. However, liquid potassium chloride products, which pose little or no safety problem in regard to gastrointestinal lesions, but which are not well accepted by some patients because of the taste and inconvenience, are available in the U.S. as therapeutic alternatives.

SOMATOTROPIN (D) This is a pituitary hormone for which the sponsor submitted an IND in 1969. Clinical trials are currently ongoing to determine the effects of therapy beyond one-year in the treatment of pituitary dwarfism. Since this drug is a lyophilized human growth hormone derived from human pituitaries obtained at autopsy, the supplies are extremely limited. This limits the number of clinical trials which can be conducted. Because of the high demand for this drug in the treatment of pituitary dwarfism its wider availability would be beneficial universally.

SOTALOL This is a beta adrenergic blocking drug proposed for use as a cardiac antiarrhythmic agent. The IND was submitted by the sponsor in 1965. The sponsor voluntarily discontinued clinical investigations with this product in 1971, citing a lack of commercial promise adequate to justify the expense of developing carcinogenicity safety data. Propranolol, an acceptable alternative beta adrenergic blocking agent, is marketed in the United States.

STREPTOKINASE (D) An NDA for this enzyme was approved in 1951 for topical use to assist debriding of wounds and burns. Another sponsor is currently investigating the drug for intravenous use as a thrombolytic agent under an IND which was submitted in 1963. Because of the lack of adequate preclinical data, clinical studies were delayed, but are now proceeding. There is no drug currently marketed in the U.S. which provides safe and effective thrombolytic therapy (ability to dissolve blood clots), and this drug and urokinase (see below) are under study for this purpose under trials supported by the NIH. Both drugs have serious potential for toxicity and must be administered with great caution by experts, but they also offer the possiblity of a significant advance in the treatment of thrombotic disorders.

SULBENICILLIN (Sulfocillin) (D) An IND for this semi-synthetic penicillin was submitted in 1973. The study is in Phase II; no NDA has been submitted. The drug is similar to carbenicillin, which is approved. It is claimed to be somewhat more active than carbenicillin against Pseudomonas strains and the penicillin-resistant Straphylococcus aureus.

SULFALENE An IND for this sulfonamide antimicrobial agent was submitted in 1964 and was discontinued in 1968 for lack of interest in marketing. Subsequently two INDs were submitted for the drug in combination with trimethoprim for the treatment of malaria, and one of these INDs is still active. There are many other sulfa products on the market in the U.S. The combination of sulfamethoxazole and trimethoprim (Bactrim, Septra) is also approved.

SULPIRIDE (D) This is a pyrrol derivative for which an IND was submitted in 1973 for possible use in depression, vertigo, and gastrointestinal ulcers. It is chemically dissimilar from other antidepressant or antivertigo drugs marketed in the U.S. Sulpiride has been compared clinically with major tranquilizers of the phenothiazine group, but no advantage has been demonstrated in patients with delirium, depression or alcoholism. Investigations have not yet produced evidence of antidepressant activity equal to or better than tricyclic antidepressants marketed in the United States, such as imipramine and amitriptyline. It is too early in clinical investigations to assess the therapeutic usefulness of sulpiride, but if it proves to be a reliable antivertigo agent it would be an advantage over drugs currently marketed for vertigo; e.g., meclizine and diphenidol.

SULTHIAME This is a carbonic anhydrase inhibitor, used as an anticonvulsant, for which the sponsor submitted an IND in 1963. Subsequently NDAs for use as an anticonvulsant were submitted in 1965 and 1968. These were declared non-approvable due to a lack of data to support safety and efficacy; in particular, there was an absence of controlled clinical data. Another related carbonic anhydrase inhibitor, acetazolamide, is commercially available in this country as an anticonvulsant as well as a diuretic. No further studies with sulthiame were undertaken by the sponsor after a study supported by the National Institute of Neurologic Disease and Stroke showed the drug to be inferior to diphenylhydantoin, the most well-established alternative anticonvulsant. Sulthiame may be of some value as an adjunct to established anticonvulsants, but at the dose levels required adverse effects (primarily hyperventilation) are frequently encountered. The IND is still active, but there appears to be little interest in marketing the drug.

TAMOXIFEN (D) This estrogen-antagonist for antineoplastic use is currently being investigated at the National Cancer Institute for use in breast cancer, under an IND submitted in 1974. This class of drug is of interest because it may be as effective as such androgenic substances as testosterone while possibly avoiding some androgenic side-effects. Suitable marketed alternatives are testolactone, fluoxymesterone and calusterone. Premenopausal patients with breast cancer are usually castrated by surgery or irradiation, and drugs of this type are used only after the benefical effect of castration has ceased.

TERBUTALINE SULFATE (W) INDs for this bronchodilator were submitted in 1970 and 1974, and are still active. An NDA for the subcutaneous injection was submitted in 1973 and approved in 1974 (Bricanyl, Astra). In 1974 an NDA for the oral tablet form was submitted, and is currently under review. This drug, like albuterol (under study - see above) and metaproterenol (already approved), is claimed in some studies to offer fewer side effects than ephedrine, the most widely used oral adrenergic bronchodilator.

TETRABENAZINE This drug has chemical and pharmacological similarities to reserpine; its chemical structure even more closely resembles benzquinamide, which is marketed here as an antiemetic. Tetrabenazine has been used abroad as an anti-psychotic agent. An NDA for this indication, submitted in 1960, was withdrawn by the sponsor because of inadequacies in the preclinical data. A subsequent IND submitted by the same sponsor for a non-therapeutic clinical pharmacology study was discontinued in 1968. Recently, reports of successful treatment of certain relatively rare movement disorders (e.g., hemiballismus) have appeared, and six individual investigators have filed INDs for this use in the last four years. The drug in some patients appears, however, to cause depression so severe as to require its discontinuation. The drug may have promise, since there currently are no effective drugs marketed for the uncommon neurologic disorders for which it has been proposed.

THIOCARLIDE This antituberculous drug is also known as Amixyl, Dantanil, Disocarban, Isoxyl, DAT and Sarbamyl. An IND for Isoxyl was filed in 1963 and was discontinued in 1967 because the sponsor stated that it was "too costly to research." Another IND was filed in 1968 by a foreign firm and was subsequently discontinued in 1972; no reason for discontinuing was submitted. There are several approved antituberculous drugs available in the U.S. and no known advantages of this drug.

THIOGUANINE Fully approved NDA (1966) Thioguanine Tabloid (Burroughs-Wellcome) - antineoplastic.

THIOPHENICOLGLYCINATE (D) An IND for this antibiotic was first submitted in 1964 but was discontinued for lack of commercial interest. This drug is similar to chloramphenicol, which has long been marketed in the U.S.

THYROTROPIN-RELEASING HORMONE (D) This is a hypothalamic thyroid stimulating hormone prepration for which several INDs were submitted in 1970, 1971, 1973, and 1974. A commercial sponsor submitted an NDA for this product in 1974, which is currently under active review. This drug may prove to be useful in the diagnosis of disorders of the thyroid and pituitary gland.

TILIDINE (D) This is a strong analgesic for which INDs were submitted by the sponsor in 1968 and 1970. The clinical trials under this IND are currently in progress, but research has not progressed rapidly. There are acceptable alternative drugs marketed in the U.S. for this indication, such as morphine, meperidine, and pentazocine. Claimed advantages of tilidine are that it may have a lesser abuse potential than morphine, that it is synthetic and therefore does not require raw opium as a source for chemical synthesis, and that it may produce less respiratory depression than narcotic analgesics.

TIMOLOL This beta adrenergic blocking agent has been proposed for use as a cardiac antiarrhythmic agent. It is claimed to have a superior margin of safety (e.g., myocardial depression versus beta blockade) over propranolol. An IND was submitted by the sponsor in 1970. As with other beta adrenergic blocking drugs, ongoing clinical trials are limited to 30 days pending the results of animal carcinogenicity studies. Such studies have been completed and are at present in the process of analysis. The beta adrenergic blocking drug, propranolol, is available on the market for the same proposed use.

TOFENACIN This drug, proposed as an antidepressant, is related to marketed antihistamines, anticholinergics, and so-called muscle relaxants, such as orphenadrine. An IND was submitted in 1969, but was subsequently discontinued by the sponsor. Reports of clinical trials do not suggest superiority to existing alternative antidepressants such as imipramine or amitriptyline, and raise questions as to effectiveness. The chemical and pharmacological differences of tofenacin from available antidepressants, however, suggest the theoretical possiblity of fewer adverse effects.

TRANEXAMIC ACID (D) An IND was filed in 1969 for this anti-fibrinolytic coagulant. Because of severe toxic effects in animals, including retinal atrophy at all dose levels, clinical studies are at present limited to a rare condition, hereditary angioneurotic edema, for which there is no good alternative therapy.

TRAZODONE (D) This drug is a triazolopyridine derivative, proposed as an antidepressant, without obvious structural similarity to other drugs with this activity. A research sponsor submitted an IND in early 1974, and clinical trials are now in progress. No commercial IND has been filed. It is too early to determine possible therapeutic advantages of trazodone. There are alternative antidepressants available, such as imipramine and doxepine.

TRIBENOSIDE (D) An IND was submitted in 1967 for evaluation of this drug as a systemic anti-inflammatory agent in the symptomatic treatment of varicose syndromes including hemorrhoids. The clinical studies did not establish effectiveness and the drug was shown to be allergenic in a notable percentage of cases. The IND was discontinued in 1972. Many oral analgesic agents as well as local remedies are marketed in the United States for relief of the discomfort due to hemorrhoids.

TRIFLUPERIDOL This is a butyrophenone anti-psychotic tranquilizer for which one sponsor submitted several INDs for different formulations in 1963. All of these INDs were discontinued by the sponsor in 1967 and 1968, due to a lack of marketing interest. A closely related drug marketed in the U.S. for this indication by the same sponsor is haloperidol. Other available anti-psychotic drugs include the various phenothiazine tranquilizers. Therapeutic advantages of trifluperidol over available alternatives are not apparent.

TRIMETHOPRIM-SULFAMETHOXAZOLE (W) Fully approved NDA (1973) Bactrim (Hoffmann-LaRoche), Septra (Burroughs-Wellcome) anti-infective combination for chronic urinary tract infections only; other possible indications are being investigated under INDs.

TRIMIPRAMINE MALEATE This tricyclic dibenzazepine anti-depressant is structurally very similar to imipramine. An IND was submitted in 1964 for its use as an anti-depressant. In 1968, the sponsor submitted an NDA, which has been declared non-approvable due to a lack of data resulting from adequate and well-controlled clinical trials. Other drugs in the same chemical class marketed in the U.S. for this indication are imipramine hydrochloride and amitriptyline hydrochloride, and this drug appears to provide no real therapeutic advantage.

UROKINASE (D) This fibrinolytic agent has been proposed for use in the treatment of venous thrombosis. Three sponsors submitted INDs, in 1963, 1964 and 1971. Investigations have not proceeded beyond Phase II studies, primarily because of difficulties in producing satisfactory material from its source, which is human urine. The material is now being derived from a new source, human embryonic kidney cell cultures, which promises to facilitate future study. Inherent advantages in its mode of action are anticipated if effectiveness is demonstrated. There is no drug currently marketed in the U.S. which provides safe and effective thrombolytic therapy (ability to dissolve blood clots), and this drug and streptokinase (see above) are under study for this purpose under trials supported by the NIH. Both drugs have serious potential for toxicity and must be administered with great caution by experts, but they also offer the possibility of a significant advance in the treatment of thrombotic disorders.

VERAPAMIL This is a coronary vasodilator proposed for use in angina pectoris. The sponsor submitted an IND in 1968, but clinical investigation was discontinued in 1970 due to the appearance of cataracts in dogs. Patients who received this investigation drug have been followed by the sponsor ophthalmologically for two years. A report on the final results of the examinations has been requested. Alternative treatment, such as nitroglycerine, is available for angina.

XANTHINOL NIACINATE This is a vasodilator proposed for the treatment of peripheral vascular disease. An IND was filed in 1963 and an NDA in 1964. Following notification that the application was incomplete because of a lack of documentation of safety and efficacy, it was withdrawn by the sponsor in 1967. Peripheral vasodilator drugs which are currently marketed have been declared "possibly effective" pending the results of new studies. A truly effective peripheral vasodilator would be a therapeutic advance.

NO IND IN U.S.

Acefylline Piperazine*
Ajmaline, N-Propyl-, Hydrogen T (D)
Alcuronium Chloride
Alphaloxone and Alphadolone
Ampicillin Potassium*
Bencyclane Fumarate (D)
Betamethasone (Inhaler) (W)
Benziodarone +
Clomocycline
Cactinomycin*
Chinolymethylene Diphenol (D)
Cicrotoic acid
Clobetasol Propionate (D)
Cyclofenil (D)
Deglycyrrhizinated Licorice (W)
Depressin (D)
Dobesilate Calcium (D)
Dosulepin HCl
Etodroxizine Dimaleate (D)
Febutolo (D)
Floredil HCl (D)
Formocortal Acetate
Gefarnate
Guanoclor Sulfate (W)
Hexoprenaline (D)
Homofenazine (D)
Hydrotalcite (D)
Ibufenac +
Indomethacin Meglumine* (D)
Ioglycamate Meglumine (D)
Ioxithalamic Acid (D)
Ketophenylbutazone (D)
Ketoprofen (D)
Lithium Sulfate* (D)
Lymecycline
Metiazinic Acid (D)
Mitobronitol
Moxisylyte HCl
Naftazone (D)
Nitrimidazine (Nimorazole)
Noleptam (D)
Pacilan (D)
Penflutizide (Penfluzide) (D)
Pengitoxin (D)
Phenoperidine HCl
Phenylpentanol (D)
Phenylprenazone (D)
Picosulfol (D)
Polidexide
Prothionamide
Proxyphylline
Pryibenzyl Methylsulfonate (D)
Pyrissuccideanol Maleate (D)
Pyritinol (D)
Pyrrolidine (D)
Spicillin (D)
Steroderm (D)
Sulfaguanol (D)
Thiambutosine
Tolperisone HCl (D)
Trimetazidine
Tromantadine HCl (D)
Trophosphamide (Trofosfamide) (D)
Vascoril (D)
Vincamine (D)
Vinquidil HCl (D)

* Identified as salt, ester or other form or combination of U.S.-marketed drug(s)

+ Marketing discontinued in other countries because of toxicity

APPENDIX C

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DANTROLENE SODIUM FOR TREATMENT OF SPASTICITY

Dantrolene sodium (Dantrium - Eaton), a new oral hydantoin derivative, is advertised as "The first specific [drug] for skeletal muscle spasticity resulting from serious chronic disorders (not indicated for rheumatic spasm)." Dantrolene is recommended by the manufacturer for patients with spasticity resulting from such conditions as stroke, spinal injuries, multiple sclerosis, or cerebral palsy.

MODE OF ACTION - Dantrolene apparently acts directly on the contractile mechanism of skeletal muscle (K. O. Ellis et al., J. Pharm. Sci., 62:948, 1973; J. V. Putney, Jr., and C. P. Bianchi, J. Pharmacol. Exp. Ther., 189:202, April 1974). The drug probably acts by interfering with release of calcium from the sarcoplasm; it is the released calcium that is responsible for initiating muscular contraction.

CLINICAL STUDIES - In a study that included 10 patients with weakness or paralysis resulting from stroke or cord lesions, all 10 showed some degree of improvement in spasticity while taking dantrolene. In this same study, motor performance also improved in some patients, but in others it became worse, possibly because spasticity may sometimes help motor function (S. B. Chyatte and J. V. Basmajian, Arch. Phys. Med. Rehabil., 54:311, 1973). In a study of 17 patients with athetoid cerebral palsy, eight patients showed moderate improvement while taking the drug. One 11-year-old boy with postencephalitic athetosis and dystonia improved dramatically (S. B. Chyatte et al., Arch. Phys. Med. Rehabil., 54:365, 1973). Of 20 patients with multiple sclerosis treated with dantrolene for five weeks in a double-blind crossover trial, six seemed to benefit, but weakness occurred in 15 of the 20. Two patients developed severe weakness and no benefit (A. J. Gelenberg and D. C. Poskanzer, Neurology, 23:1313, 1973). One Medical Letter consultant with extensive experience using dantrolene reports that patients with amyotrophic lateral sclerosis tend to complain of increased weakness without accompanying benefit.

ADVERSE EFFECTS - The most important adverse effect of dantrolene is weakness. When patients are already paraplegic, drug-induced weakness may make little difference. In other patients, however, it can be disabling; weakness is sometimes accompanied by severe apathy. Diarrhea is a frequent adverse effect, and vertigo can also be troublesome. Hepatic dysfunction has been reported in a few cases, and phototoxicity may occur. The adverse effects of using dantrolene for more than one year are not known.

DOSAGE - A starting dose of 25 mg of dantrolene twice daily is gradually increased by adding 50 to 100 mg daily each week, to a maximum of 400 mg daily. In children, the recommended starting dose is 1.0 mg/kg of body weight twice daily, increasing to a maximum of 3.0 mg/kg four times a day, but not to exceed 400 mg daily. Beneficial effects may not appear before a week or more of treatment.

CONCLUSION - Dantrolene seems to be an effective oral drug for treatment of some forms of spasticity, but a drug that produces weakness while reducing spasticity is not ideal. Dantrolene is most likely to be helpful when spasticity is painful or is the limiting factor in recovery of function, but its exact role in the treatment of various spastic disorders remains to be established.

HYCANTHONE FOR SCHISTOSOMIASIS

Schistosomiasis occurs in millions of people in South America, Africa, the Middle East, and Asia. In the United States, the disease is usually found only in patients from Puerto Rico, in Peace Corps volunteers, in travelers from abroad, and in recent immigrants.

Control of the infection can be achieved by destruction of the snails that are intermediate hosts for the worms, and through sanitary engineering projects, improved personal hygiene, and the use of such drugs as niridazole (Ambilhar - Ciba, Switzerland), stibophen (Fuadin - Winthrop), and antimony sodium dimercaptosuccinate (Astiban - Hoffmann-La Roche, Switzerland).

HYCANTHONE - Another drug manufactured by Winthrop, hycanthone, has not been submitted for approval to the U.S. Food and Drug Administration, but is widely promoted and used in Latin America and elsewhere. High, though variable, cure rates have been reported in infections caused by Schistosoma mansoni and S. haematobium (WHO Tech. Rep. Ser., No. 515, 1973). The drug is not useful in S. japonicum infections. It had been hoped that hycanthone would cure schistosomiasis with a single intramuscular injection, but some patients require repeated injections, and others who appear to have been cured suffer relapses with worms that are resistant to the drug.

HEPATIC DAMAGE - Acute fatty liver that appears a few days after administration of the drug and leads to death is the most serious immediate adverse effect of hycanthone. Estimates of the frequency of this complication vary from one death per thousand patients to one per 18,000 patients. The mechanism of this reaction is not known.

TERATOGENICITY - Hycanthone in higher than recommended doses has been found to be teratogenic in animals. There are no reports of hycanthone-associated malformations in the human fetus, but extensive studies have not been done.

CARCINOGENICITY - F. M. Hetrick and W. L. Kos (J. Pharmacol. Exp. Ther., 186:425, 1973) reported that exposure of some virus-infected cell cultures to concentrations of hycanthone as low as 0.1 μg/ml resulted in malignant transformations. Hepatocellular carcinomas have been found in mice infected with S. mansoni and treated with a single dose of hycanthone, but not in uninfected mice treat-

ed with hycanthone (W. H. Haese et al., J. Pharmacol. Exp. Ther., 186:430, 1973). Other workers, from the Sterling Winthrop Research Institute, were unable to demonstrate carcinogenicity of hycanthone in infected mice (A. Yarinsky et al., Toxicol. Appl. Pharmacol., 27:169, 1974).

CONCLUSION - Hycanthone is used in many parts of the world for treatment of some forms of schistosomiasis. Although it had been hoped that it would provide a "one-shot" cure for the disease, many patients require repeated treatment with the drug and some develop infections with hycanthone-resistant organisms. Whether the convenience and relatively high cure rate of hycanthone outweigh the risks of hepatic necrosis, teratogenicity, and carcinogenicity may take many years to establish. Since alternative drugs are available, administration of hycanthone to children and other patients with a long life expectancy should be avoided.

SYSTEMIC REACTIONS TO HYMENOPTERA STINGS

Local reactions to insect stings such as swelling, redness, itching, and pain may be caused by direct injury from enzymes or toxins in the insect's venom. Systemic reactions, usually allergic in origin, include urticaria, bronchospasm, laryngeal edema, abdominal pain, anaphylactic shock, and death. The most severe systemic effects are caused by reactions to the stings of Hymenoptera, including bees, wasps, hornets, and yellow jackets. Some patients who have had systemic reactions to these stings apparently lose their sensitivity and can tolerate a subsequent sting from the same species of insect without difficulty, but there is no way of predicting in which patients this will happen.

EMERGENCY TREATMENT - The most effective immediate treatment for systemic reactions to Hymenoptera stings is subcutaneous injection of 0.3 ml of 1:1000 epinephrine (0.1 to 0.2 ml for children). Parenteral or oral administration of antihistamines, corticosteroids, or ephedrine is no substitute for epinephrine, but these drugs may be used to help prevent a return of symptoms as the effect of epinephrine wears off; corticosteroids are not effective until several hours after administration. Commercial kits containing a syringe of epinephrine are available (Ana-Kit - Hollister-Stier, Spokane, Washington; "Personal" Insect Sting Kit - International Medication Systems, South El Monte, California). Ice packs can slow the absorption of venom and also relieve pain.

DESENSITIZATION WITH WHOLE-INSECT EXTRACTS - The only materials commercially available for testing sensitivity to Hymenoptera, and for desensitizing patients, are monovalent and polyvalent extracts of the whole bodies of bees, wasps, hornets, and yellow jackets. Since the patient's identification of the stinging insect is often unreliable, most allergists use the polyvalent preparations. These extracts are probably useless for the diagnosis of Hymenoptera sensitivity (H. J. Schwartz, JAMA, 194:703, 1965), and the effectiveness of desensitization with whole-body extracts has never been convincingly demonstrated by controlled trials. Deaths from stings have occurred in some patients who previously had a series of desensitizing injections with whole-body extracts (J. H. Barnard, J. Allergy Clin. Immunol., 52:259, 1973). In spite of reservations about their effectiveness, most Medical Letter consultants recommend desensitization with whole-body Hymenoptera extracts for patients who have had systemic reactions to Hymenop-

tera stings, since no effective alternative treatment is generally available. Local reactions, however severe, are not an indication for such injections.

INVESTIGATIONAL USE OF HYMENOPTERA VENOMS - Most Medical Letter allergy consultants would prefer to use the Hymenoptera venom alone rather than whole-body extracts in patients who have had systemic reactions to stings, both for specific diagnosis (A. K. Sobotka et al., J. Allergy Clin. Immunol., 53:170, March 1974) and for desensitization (M. H. Loveless and W. R. Fackler, Ann. Allergy, 14:347, 1956; L. M. Lichtenstein et al., N. Engl. J. Med., 290:1223, May 30, 1974). Unfortunately, the use of these venoms is still in the investigational stage, and they are not available commercially; patients who have had a severe anaphylactic reaction to a Hymenoptera sting should be referred to a clinical immunology center where desensitization with venom could be considered.

CONCLUSION - Patients who have had systemic reactions to Hymenoptera stings should carry syringes containing 0.3 ml of 1:1000 epinephrine for emergency treatment. Until Hymenoptera venoms become generally available for diagnosis and desensitization, such patients should be immunized against future reactions with whole-body extracts of Hymenoptera.

TRAVELERS' WARNING: DIPYRONE IN OVER-THE-COUNTER DRUGS

Almost 10 years ago, The Medical Letter warned travelers that the analgesic and antipyretic drugs aminopyrine and dipyrone, noted for their ability to produce fatal blood dyscrasias, were "available under various names without prescription in many European and Latin American countries..." (Vol. 6, p. 104, 1964). Unfortunately, in 1974, medicines containing dipyrone are still widely sold in some Latin American countries, according to a bulletin from the International Desk of Consumers Union.

BRAND NAMES AND COMPANIES - Dipyrone (dipirona) is sold in Latin America, for example, by Upjohn as Alginodia, by Winthrop as Conmel, by McKesson as Dipirona MK, and by Hoechst as Novalgina. It is also marketed in such combination drugs as Baralgin (Hoechst), Beserol (Winthrop), Buscapina Compositum (Boehringer), Corticidin S/A and Corilin Pediatrico Supositorios (Schering), Dipirona MK Compuesta (McKesson), Dorflex (Merrell), and Valpirone (Endo).

AVAILABILITY AND WARNINGS - In many countries, these drugs are readily available in drugstores without prescription, with no warnings to physicians, pharmacists, or patients. Some products carry warnings of possible serious harmful effects, but the labeling sometimes also states that the drug can be used for such minor ailments as colds or toothaches.

CONCLUSION - Physicians should warn patients planning to travel outside the United States that dipyrone, a drug that can cause fatal blood dyscrasias, is sold without prescription in other parts of the world. Physicians should suggest that travelers carry a small supply of aspirin or acetaminophen purchased in the United States for headaches and minor aches and pains, rather than rely on "aspirin-like" compounds obtained elsewhere.

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THE WASHINGTON POST
K6 Sunday, June 9, 1974

Realizing Some of the Risks in Taking Foreign Pharmaceuticals

By Morton Mintz

Americans who become ill in a foreign country run a serious risk of taking medicines that are banned in the United States because they have not been demonstrated to be safe, or because they have not been shown to be effective in the conditions for which they are recommended.

My family was exposed to the problem in Spain last summer, when all of us developed mild and, as it turned out, short-lived stomach upsets.

An American friend steered my wife to an English-speaking pharmacist who, after listening attentively to her description of the ailment, sold her eight capsules of Chlorostrep.

A so-called fixed-ratio combination, Chlorostrep consists of equal amounts of two antibiotics which, in the United States, can be dispensed only on prescription of a physician. The producer is Parke-Davis, an American firm.

One of the antibiotics, dihydrostreptomycin, has long been known to cause serious side effects in some users, including irreversible deafness.

The other ingredient is Chloromycetin, Parke-Davis's trade-name for chloramphenicol. Depending on dosage, it can cause fatal aplastic anemia in one user in 24,200 to one in 40,500. Because it is so hazardous, it is supposed to be reserved only for typhoid fever, for hemophilus influenzae meningitis and for rare conditions in which the usual drugs of choice cannot be used.

For several years now, no product such as Chlorostrep has been permitted on the American market. Why? Because all fixed combinations of antibiotics were unanimously condemned by 30 specialists in the treatment of infectious diseases who reviewed them for the National Academy of Sciences and the Food and Drug Administration.

The specialists declared such mixtures to be therapeutically irrational, because they are no more effective than their components used separately, and because it is hazardous to use two potent drugs where one suffices, or to use more antibiotics than necessary. Obviously, a person using a combination cannot ingest a needed ingredient without also swallowing an un-needed one, or to increase the dose of a needed component without also increasing the dose of an un-needed one.

"Chlorostrep consists of equal amounts of two antibiotics which, in the United States, can be dispensed only on prescription of the physician. The producer is Parke-Davis, an American firm. One of the antibiotics has long been known to cause serious side-effects in some users."

The importance of this advice is illustrated by a fixed antibiotic combination trade-named Panalba. It once was said by the then-commissioner of the FDA, Dr. Herbert L. Ley Jr., to be causing hundreds of thousands of needless injuries, a few of them fatal, each year.

Ironically, the fault lay with the secondary component, novobiocin, that was found in studies actually to be detracting from the efficacy of the primary ingredient, tetracycline. After a long court fight by the FDA here, the manufacturer, the Upjohn Co., was forced to stop selling the combination here—but continued to sell it abroad, under the name Albamycin-T.

In Columbia, "you can buy any drug at any pharmacy," a Columbian, Alberto Donadio of Medellin, said in a recent letter to this reporter.

Donadio specifically cited DES (diethylstilbesterol), which has been widely prescribed to prevent miscarriages although substantial evidence of efficacy is lacking.

In 1971, researchers at Massachusetts General Hospital made the discovery of sometimes fatal vaginal cancer in numerous daughters of women who more than 20 years earlier had taken DES in pregnancy.

The package brochure in Columbia "carries no notice of side effects," Donadio said. He recalled that his inquiry about such regulatory laxity to a ministry of health official elicited the reply that "Columbia is a sovereign country."

In London on May 13, The Guardian disclosed a comparative study by reporter Adam Raphael showing that of the 400 medicines ruled by the American FDA to be lacking evidence of effectiveness, nearly one-fourth are still on sale in Britain. Three examples:

• Bradasol lozenges, promoted in Britain by CIBA as "effective in extreme dilutions against the majority of bacterial and fungal organisms causing throat and mouth infections," but withdrawn from the United States because CIBA did not provide the FDA with what it deemed "substantial evidence of effectiveness" for such claims.

• Benylin expectorant, one of the most frequently prescribed cough medicines in England. Parke-Davis claims Benylin gives "comprehensive relief to the coughing patient." The FDA, in a ruling the firm is contesting, said it lacks adequate evidence of efficacy for all of the conditions Benylin is claimed to treat.

• Sinaxar, withdrawn from the United States market because the producer, Armour, could not substantiate claims of effectiveness, is promoted in Britain as a drug that "releases the victim of muscle spasm, relieves pain, promotes normal activity" and "is consistently effective."

In Spain, the Parke-Davis instruction leaflet for Chlorostrep advises against use in "infecciones triviales."

Of course, trivial infections were precisely what my family had. But how many American tourists, even those able to read Spanish, would be inclined to heed the labeling once they have consulted a kindly and supposedly knowledgeable pharmacist? How many might have known that paregoric, the old standby from grandmother's day, is still the drug of choice for a mild, self-limiting gastro-intestinal upset?

Well, we were lucky. Not so a 35-year-old British mother of three. Vacationing in Spain, she had a minor respiratory infection. She "treated herself with a bottle of medicine bought

(continued)

from a chemist's shop," doctors reported in Lancet.

"The preparation contained a total of 3.15 grams of chloramphenicol . . . The coroner's report on the death stressed the danger of easily obtainable chloramphenicol . . . for the protection of the many holiday-makers we are concerned to give as much publicity as possible to this situation."

In 1972, the International Organization of Consumers Unions obtained from 21 countries a total of 55 packages of chloramphenicol in which a manufacturer had enclosed an instructional leaflet.

The countries included four—Egypt, Greece, Thailand and Turkey—where chloramphenicol is sold without prescription. In contrast, New Zealand allows it to be dispensed only on the advice of a specialist—a policy tougher than our own.

Packages of Cholormycetin, the most widely distributed brand, came from 11 of the 21 countries with instruction brochures, but without them from four. The survey included two or more samples of only four other brands, each listed with the manufacturer in parenthesis:

Paraxin (Boehringer) and Synthomycetine (Lepetit), each from four countries; Detreomycine (Tolfa), from three countries, and Kemicetine (Carlo Erba), from two countries.

"In general, little or no information was given on the bottle or pack containing the drug," the committee reported in Lancet last Oct. 6. "In a few cases a list of recommended uses (indications) and a brief warning were printed on the carton. The chief source of information was thus the package insert. Here are other highlights of the survey:

• Of the 55 leaflets, seven listed no indications at all. Generally the listed indications varied widely, among countries and, as well, among different brands from the same country.

• Parke-Davis leaflets for Caloromycetin listed indications that also varied widely among various countries (although the company "told us that they are now introducing more standardized instructions"). The most restrictive indications, those approved for the United States, were also the leaflets for Chloromycetin manufactured in the United Kingdom for use there and in Finland and Switzerland.

• Contra-indications—circumstances in which a drug should not be used—and warnings also varied widely among countries and among different brands within a country.

"In general, those brands which had the narrowest indications also had the strictest warnings," the Lancet report said. "Most serious is that no less than seven brands (three of them from Greece) listed no contra-indications or warnings at all. One leaflet from Greece claimed that the drug was free from all side-effects.

"Another unsatisfactory feature that emerged was the multitude of different headings under which the warnings were given. They included: 'attention,' 'caution,' 'contra-indications,' 'dose' 'neurology,' 'precautions,' 'side-effects,' 'side reactions,' 'tolerance,' 'warning,' and simply 'NB' [nota bene] (note well).

"As for indications, the contra-indications and warnings found with Parke-Davis Chloromycetin, at the time of our survey, varied from country to country. That distributed in the United States included warnings for all three of the conditions we list (allergy or hypersensitivity, blood and gastrointestinal upsets) and for six out of the eight contra-indications. In West Germany and Australia, however, Chloromycetin instructions then carried only one warning under blood and no contra-indications at all."

The authors of the Lancet article, four members of the Research Institute for Consumer Affairs in London, said there is "urgent need for stricter control of the availability of chloramphenicol."

They urged that every country ban its sale except by prescription, that the recommended uses be confined to those diseases "where no effective and safe alternative is available," that the warnings be standardized and that the World Health Organization consider making information on the drug easily available to its member countries.

But for drugs as a whole, American tourists generally will continue to run needless risks abroad so long as other nations do not protect their own citizens with laws and enforcement mechanisms comparable to our own.

The writer reports on consumer affairs for The Washington Post.

Medicine: A Warning

By Morton Mintz

Physicians should warn patients planning to travel in Latin America that medicines containing dipyrone, a painkiller that can cause fatal blood diseases, is widely sold there, without prescription and "with no warnings to physicians, pharmacists or patients," The Medical Letter says in its July 19 issue.

Doctors should suggest to travelers that they carry a small supply of aspirin or acetaminophen purchased in the United States for headaches and minor aches and pains, rather than rely on "aspirin-like" compounds obtained elsewhere, the nonprofit bi-weekly says.

The publication recalled that it had warned travelers 10 years ago that dipyrone and another so-called antipyretic (antifever) agent, aminopyrine were "available under varius names without prescription in many European and Latin American countries."

"Unfortunately, in 1974, medicines containing dipyrone are still widely sold in some Latin American countries, according to a bulletin from the International Desk of Consumers Union," The Medical Letter said.

For example, it said, dipyrone or diprionа, is sold in Latin America by the Upjohn Co., under the trade-name Alginodia, by Winthrop (Sterling Drug) as Cammel, by McKesson Laboratories as Dipirona MK, and by Hoechst Pharmaceuticals as Novalgina.

In addition, dipyrone appears in combination with other drugs in Hoechst's Baralgin, Winthrop's Beserol, Boehringer's Buscapina Compositum, Schering's Coricidin S/A and Corilin Pediatrico Supositorios, McKesson's Dipirona MK Compuesta, Merrell's Dorflex and Endo's Valpirone.

"Some products carry warnings of possible serious harmful effects, but the labeling sometimes also states that the drug can be used for such minor ailments as colds or toothaches," says The Medical Letter, which evaluates drugs for physicians.

The Council on Drugs, a scientific panel which the American Medical Association dissolved last year, said in its authorative "AMA Drug Evaluations: 1971" that because of its ability to cause sometimes fatal blood diseases, the use of dipyrone as a general analgesis, antiarthritic or routine antipyretic "cannot be condoned."

The writer reports on consumer news for The Washington Post.

Senator KENNEDY. The subcommittee hearings now stand adjourned.

[Whereupon, at 1:03 p.m., the subcommittee adjourned.]