

November 2006

PRESCRIPTION DRUGS

Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising



G A O

Accountability * Integrity * Reliability



Highlights of [GAO-07-54](#), a report to congressional requesters

Why GAO Did This Study

The Food and Drug Administration (FDA) is responsible for overseeing direct-to-consumer (DTC) advertising of prescription drugs. If FDA identifies a violation of laws or regulations in a DTC advertising material, the agency may issue a regulatory letter asking the drug company to take specific actions. GAO was asked to discuss (1) trends in drug company spending on DTC advertising and other activities; (2) what is known about the relationship between DTC advertising and drug spending and utilization; (3) the DTC advertising materials FDA reviews; (4) the number of regulatory letters that cited DTC materials and FDA's process for issuing those letters; and (5) the effectiveness of these letters at limiting the dissemination of violative DTC advertising. GAO reviewed research literature, analyzed FDA's processes, and examined FDA documentation.

What GAO Recommends

GAO recommends that FDA (1) document criteria for prioritizing DTC materials for review, (2) systematically apply its criteria to materials it receives, and (3) track which materials it reviews. In its comments on a draft of this report, HHS disagreed with the recommendations, stating that they would require vastly increased staff. GAO believes that FDA already has most of the information that would be required to establish a systematic process for screening DTC materials.

www.gao.gov/cgi-bin/getrpt?GAO-07-54.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse at (202) 512-7119 or crossem@gao.gov.

PRESCRIPTION DRUGS

Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising

What GAO Found

Drug company spending on DTC advertising—such as that on television and in magazines—of prescription drugs increased twice as fast from 1997 through 2005 as spending on promotion to physicians or on research and development. Over this period, drug companies spent less each year on DTC advertising (\$4.2 billion in 2005) than on promotion to physicians (\$7.2 billion in 2005) or research and development (\$31.4 billion in 2005).

Studies GAO reviewed suggest that DTC advertising has contributed to increases in drug spending and utilization, for example, by prompting consumers to request the advertised drugs from their physicians, who are generally responsive to these requests. Evidence suggests that the effect of DTC advertising on consumers can be both positive, such as encouraging them to talk to their doctors, and negative, such as increased use of advertised drugs when alternatives may be more appropriate.

FDA reviews a small portion of the DTC materials it receives. To identify materials that have the greatest potential to impact public health, FDA has informal criteria to prioritize materials for review. However, FDA has not documented these criteria, does not apply them systematically to all of the materials it receives, and does not track information on its reviews. As a result, the agency cannot ensure that it is identifying or reviewing those materials that it would consider to be the highest priority.

FDA has taken longer to draft and review regulatory letters and the agency has issued fewer letters per year since 2002, when legal review of all draft regulatory letters was first required. From 2002 through 2005, from the time FDA began drafting a regulatory letter for a violative DTC material, it took the agency an average of 4 months to issue a regulatory letter, compared with an average of 2 weeks from 1997 through 2001. FDA has issued about half as many regulatory letters per year since the 2002 policy change.

The effectiveness of FDA's regulatory letters at halting the dissemination of violative DTC materials has been limited. The 19 regulatory letters FDA issued in 2004 and 2005 were issued an average of 8 months after the materials were first disseminated. By the time FDA issued these letters, companies had already discontinued use of more than half of the violative materials. When the cited materials were still being disseminated, drug companies complied with FDA's requests to remove the materials, and identified and removed other materials with similar claims. FDA's issuance of regulatory letters did not always prevent drug companies from later disseminating similar violative materials for the same drugs. These issues are not new. In 2002, GAO reported that, by delaying the issuance of regulatory letters, the 2002 policy change had adversely affected FDA's ability to enforce compliance. At that time, GAO recommended, and FDA agreed, that letters be issued more quickly. GAO continues to believe this is necessary in order to limit consumers' exposure to false or misleading advertising.

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Abbreviations

DDMAC	Division of Drug Marketing, Advertising, and Communications
DTC	direct-to-consumer
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
OCC	Office of the Chief Counsel
PhRMA	Pharmaceutical Research and Manufacturers of America

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United States Government Accountability Office
Washington, DC 20548

November 16, 2006

The Honorable Bill Frist
Majority Leader
United States Senate

The Honorable Charles E. Grassley
Chairman
Committee on Finance
United States Senate

The Honorable Herbert Kohl
Ranking Minority Member
Special Committee on Aging
United States Senate

Spending on prescription drugs, which accounted for about 11 percent of total health care spending in 2004,¹ has increased more rapidly since 1997 than any other component of health care spending in the United States. One factor, among many, that has been cited as contributing to this trend is the advertising of prescription drugs directly to consumers. Direct-to-consumer (DTC) advertising includes a range of media, such as television, radio, magazines, newspapers, and the Internet.² The pharmaceutical industry spent more than \$4.2 billion in 2005 to advertise prescription drugs to consumers.³ Supporters of DTC advertising maintain that it educates consumers, helps to get patients into needed treatment, and

¹Centers for Medicare & Medicaid Services, "Highlights," *National Health Expenditure Data, Historical* (Baltimore, Md.: Centers for Medicare & Medicaid Services, 2006), <http://www.cms.hhs.gov/NationalHealthExpendData/> (accessed July 31, 2006).

²In addition to DTC advertising, drug companies promote their drugs through other consumer-directed materials—such as informational videos or brochures—that are intended to be given to consumers by medical professionals. Drug companies also promote prescription drugs to medical professionals, primarily by using sales representatives to provide information about prescription drugs and by advertising in professional journals. Further, drug companies provide free samples of prescription drugs that medical professionals can give to their patients.

³IMS Health Inc., "Total U.S. Promotional Spend by Type, 2005," *Top-Line Industry Data* (Fairfield, Conn.: IMS Health Inc., 2006), <http://www.imshealth.com/> (accessed Aug. 21, 2006).

saves money by reducing spending on other medical care. Critics contend that it can be misleading, encourages inappropriate increases in prescription drug use, and creates unnecessary costs for the U.S. health care system.

The Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) regulates the promotion and advertising of prescription drugs, including DTC materials and materials directed to medical professionals, to ensure that they are not false or misleading and otherwise comply with applicable laws and regulations.⁴ This oversight function is carried out by the Division of Drug Marketing, Advertising, and Communications (DDMAC) within FDA's Center for Drug Evaluation and Research.⁵ FDA regulations require that drug companies submit final advertising materials to FDA at the time they are first disseminated to the public.⁶ In addition, drug companies sometimes voluntarily submit draft versions of DTC advertising materials to FDA prior to their release in order to obtain advisory comments from the agency.

If FDA identifies a violation in a disseminated DTC advertisement, such as a false or misleading safety or effectiveness claim, the agency may issue a regulatory letter. In these letters, FDA asks drug companies to take specific actions such as stopping the dissemination of the advertisement and, if FDA finds the violation to be particularly serious, running another advertisement to correct misleading impressions left by the violative advertisement. Regulatory letters for these violative advertisements are drafted by DDMAC. Since January 31, 2002, at the direction of HHS, all draft FDA regulatory letters, including the letters drafted by DDMAC, are reviewed and approved by FDA's Office of the Chief Counsel (OCC) before they are issued in order to ensure the letters' "legal sufficiency and

⁴See 21 U.S.C. § 352(n), 21 C.F.R. § 202.1(e)(2006). FDA's authority does not extend to "help-seeking" advertisements—those that do not identify prescription drugs by name, but rather discuss a disease or condition and advise the audience to "see your doctor" for possible treatments. In addition, the Federal Trade Commission has primary oversight responsibility for the regulation of advertising for over-the-counter drugs.

⁵Other centers within FDA are responsible for overseeing promotion and advertising of biologics—such as vaccines and blood products—and electronic products emitting radiation.

⁶21 C.F.R. § 314.81(b)(3)(i)(2006).

consistency with agency policy.”⁷ In October 2002, we reported that the 2002 policy change had adversely affected FDA’s ability to enforce compliance with its regulations by delaying the issuance of regulatory letters and potentially allowing misleading advertisements to continue to be disseminated.⁸ As we noted in that report, issuing regulatory letters quickly after violative materials are disseminated is a key component of FDA’s oversight of DTC advertising because any inaccurate impressions of a drug that are caused by a misleading advertisement are minimized if the advertisement is quickly removed. We recommended that FDA take action to reduce the amount of time for internal review of draft regulatory letters citing violative DTC materials. In its response to our recommendation, FDA wrote that it had established a goal of issuing regulatory letters “within 15 working days of review at OCC.”⁹

As a result of the increased spending on prescription drugs and concerns about the effect of DTC advertising, you asked us to examine trends in DTC advertising and FDA’s regulation and oversight of this advertising. In this report, we discuss (1) trends in pharmaceutical industry spending on DTC advertising, as compared to promotion to medical professionals, and research and development; (2) what is known about the relationship between DTC advertising and prescription drug spending and utilization patterns; (3) the DTC advertising materials FDA reviews; (4) the number of FDA regulatory letters that cited DTC advertising materials and FDA’s process for issuing those letters; and (5) the effectiveness of FDA’s regulatory letters at limiting the dissemination of false or misleading DTC advertising.

To examine trends in pharmaceutical industry spending on DTC advertising, promotion to medical professionals, and research and development of new drugs, we reviewed publicly reported data. For overall drug company spending from 1997 through 2005 on DTC advertising and promotion to medical professionals, we obtained data

⁷FDA issues regulatory letters on a variety of topics as a means of bringing about voluntary compliance with applicable laws and regulations. In a November 29, 2001, memo the Deputy Secretary of HHS instructed FDA that no regulatory letters could be issued until FDA’s OCC reviewed them. According to FDA officials, OCC implemented this policy change on January 31, 2002. Prior to this policy change, OCC review and approval of draft regulatory letters before their issuance was not required.

⁸GAO, *Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations*, [GAO-03-177](#) (Washington, D.C.: Oct. 28, 2002).

⁹[GAO-03-177](#), p. 33.

from IMS Health Inc. For 2005, we reviewed detailed data from Nielsen Monitor-Plus on DTC advertising by prescription drug. Some types of promotional spending on DTC advertising and promotion to medical professionals—such as spending on professional meetings and spending on promotion to nurse practitioners—are not captured in the data we examined. In addition, we obtained data from the Pharmaceutical Research and Manufacturers of America (PhRMA)—which represents U.S. pharmaceutical research and biotechnology companies—on drug company spending for the research and development of new drugs from 1997 through 2005. Based on our review of related documentation and our discussions with the data providers, we determined that the data we present were sufficiently reliable for our use. To examine the relationship between DTC advertising and prescription drug spending and utilization, we reviewed 64 peer-reviewed journal articles, dissertations, and industry articles published from 1982 through 2006. To examine the DTC advertising materials that FDA reviews, we obtained data from FDA on the number and type of advertising materials that it received and reviewed from 1997 through 2005. Based on interviews with FDA officials and reviewers and our review of related documentation, we determined that these data were sufficiently reliable for the purposes of this report. To examine the number of FDA regulatory letters that cite violative DTC advertising materials and FDA’s process for issuing those letters, we reviewed all regulatory letters issued by FDA from 1997 through 2005 citing prescription drug promotion. We identified 135 regulatory letters issued during this period that cited one or more violative DTC advertising materials.¹⁰ We also reviewed FDA documentation on the length of the agency’s process for issuing the 135 regulatory letters. Because FDA does not track when the agency identifies a violation, we used the date on which reviewers first began drafting a regulatory letter as the earliest date in this process. To examine the effectiveness of the regulatory letters FDA issued from 2004 through 2005 that cite violative DTC advertising materials, we obtained additional details about the timeliness of the letters and drug companies’ compliance with any corrective action requested by FDA. We reviewed the content of the regulatory letters FDA issued from 1997 through 2005 to identify the violations cited; we did not evaluate the appropriateness of cited violations or evaluate the legal sufficiency of these letters. We also did not examine the effectiveness of FDA’s review of

¹⁰We excluded regulatory letters that cited only materials intended to be given to consumers by medical professionals or that cited only materials directed to medical professionals. FDA officials confirmed that the 135 letters included all letters that cited DTC materials.

draft materials at preventing potentially violative materials from being disseminated. Finally, our examination included only DDMAC's oversight of prescription drug promotion and advertising; we did not examine oversight by other parts of FDA of promotion for other types of medical products. (For additional information on our methodology, see app. I.) We conducted our work from January 2006 through November 2006 in accordance with generally accepted government auditing standards.

Results in Brief

Drug company spending on DTC advertising has increased twice as fast as spending on promotion to physicians or on the research and development of new drugs. According to publicly reported data, from 1997 through 2005, spending on DTC advertising increased almost 20 percent each year. Over the same time period, spending on drug promotion to physicians and spending on research and development each increased by about 9 percent annually. Drug companies spent less in 2005 on DTC advertising (\$4.2 billion) than on promotion to physicians (\$7.2 billion) or research and development (\$31.4 billion).

Studies we reviewed suggest that while DTC advertising increases prescription drug spending and utilization, it can have both positive and negative effects on consumers. The studies we reviewed found that increases in DTC advertising have contributed to overall increases in spending on both the advertised drug itself and on other drugs that treat the same conditions. For example, one study of 64 drugs found a median increase in sales of \$2.20 for every \$1 spent on DTC advertising. Consumer surveys suggest that DTC advertising increases utilization of drugs by prompting some consumers to request the advertised drugs from their physicians, who studies find are generally responsive to these requests. The surveys we reviewed found that between 2 and 7 percent of consumers who saw DTC advertising requested and ultimately received a prescription for the advertised drug. Studies about DTC advertising and the increased utilization of prescription drugs it can prompt suggest that its effect on consumers can be both positive, such as encouraging them to talk to their doctors about previously undiagnosed conditions, and negative, such as encouraging increases in prescriptions for advertised drugs when alternatives may be more appropriate.

FDA reviews a small portion of the DTC materials it receives, and the agency cannot ensure that it is identifying for review the materials it considers to be highest priority. Since FDA created a group in 2002—with an initial staff allocation of one group leader, four reviewers, and two social scientists—with specific responsibility for reviewing DTC materials,

the number of DTC materials FDA receives each year has almost doubled. While FDA officials told us the agency prioritizes the review of materials that have the greatest potential to impact public health, the agency has not documented criteria to make this prioritization. FDA officials identified informal criteria that reviewers consider when identifying materials for review. For example, FDA officials told us that they review all final and draft DTC television advertisements that FDA receives because these materials are likely to be widely disseminated to consumers. The agency also places a priority on draft versions of other DTC materials because this provides the agency with an opportunity to identify problems before the materials are disseminated to consumers. However, FDA does not systematically apply its informal criteria to all of the DTC materials it receives. Instead, the agency relies on reviewers to be aware of the materials the agency has received and accurately apply the various criteria to each of the materials. Furthermore, FDA cannot determine whether a particular material has been reviewed. As a result, the agency cannot ensure that it is identifying and reviewing the highest-priority materials.

Since the 2002 policy change requiring legal review of all draft regulatory letters, FDA's process for drafting and issuing letters has taken longer and the agency has issued fewer letters per year. From 2002 through 2005, once the agency began drafting a regulatory letter for violative DTC materials, it took an average of 4 months to issue the letter, while it took an average of 2 weeks to issue a letter from 1997 through 2001. FDA officials told us that the policy change contributed to the lengthened review by creating additional levels of review and making it necessary for the DDMAC reviewers who draft the regulatory letters to do substantially more work to prepare for and respond to comments from OCC. Since the policy change, FDA has issued about half as many regulatory letters citing violative DTC advertisements per year—between 8 and 11 letters annually from 2002 through 2005, compared with 15 to 25 letters annually from 1997 through 2001. FDA's regulatory letters sometimes cited more than one DTC material and more than one violation per material. Commonly cited violations included failure of the material to accurately communicate information about the safety of the drug, overstatement of the drug's effectiveness, and use of misleading comparative claims. FDA officials told us that the agency issues letters only for the violative DTC materials that it considers the most serious and most likely to impact consumers' health.

The effectiveness of FDA's regulatory letters at halting the dissemination of violative DTC materials has been limited. The 19 regulatory letters FDA issued from 2004 through 2005 were issued an average of 8 months after the violative materials were first disseminated to consumers. By the time

these regulatory letters were issued, drug companies had already discontinued use of more than half of the violative advertising materials. When cited materials were still being disseminated, drug companies complied with FDA's requests to remove the materials in response to FDA's letters. In addition, as requested in the regulatory letters, drug companies identified and removed additional materials with similar claims. Further, for the 6 letters in which FDA requested that drug companies issue new advertising materials to correct the misimpressions left by the violative materials cited in the letters, drug companies disseminated the corrective materials. These corrections were not disseminated to consumers until 5 months or more after FDA issued the regulatory letter. Despite halting the dissemination of both cited and other violative materials at the time a letter was issued, FDA's issuance of regulatory letters has not always prevented drug companies from later disseminating similar violative materials for the same drugs. We found that of the 89 drugs for which FDA cited violative DTC materials from 1997 through 2005, 25 drugs had DTC materials cited in more than one regulatory letter, sometimes for similar types of violations. In our 2002 report, we expressed similar concerns about the length of time it takes FDA to issue regulatory letters and recommended that HHS take steps to reduce the time that FDA's DTC draft regulatory letters are under review. HHS agreed in its written response to that report that letters needed to be issued more quickly and established a goal of issuing the letters "within 15 working days of review at OCC." Given our findings in this report, we continue to believe that letters must be issued more quickly in order to limit consumers' exposure to false or misleading claims.

To improve FDA's processes for identifying and reviewing final and draft DTC advertising materials, we are making recommendations to the Acting Commissioner of FDA. Specifically, we recommend that FDA (1) document criteria for prioritizing materials that it receives for review, (2) systematically apply its documented criteria to all of the materials it receives, and (3) track which materials have been reviewed.

In its comments on a draft of this report, HHS generally agreed with our description of FDA's oversight of DTC advertising but disagreed with our recommendations and some aspects of our conclusions. Specifically, HHS commented that implementing our recommendations would require vastly increased staff. HHS also expressed concern that our draft report criticized the length of time it takes to issue regulatory letters since the policy change requiring legal review, without adequately addressing the underlying purpose of that review. We believe it is important for FDA to develop a more complete and systematic process for screening the

materials it receives, in order to ensure that FDA is reviewing the highest-priority materials. We do not agree that such a process would require that every DTC material be reviewed in detail, as HHS contends. Instead, we believe that FDA should apply its criteria as a screening mechanism to all submitted materials to determine the priority of materials for review. Furthermore, FDA already has most of the information that would be necessary to establish a system to screen submitted materials against these criteria. Additionally, we agree with HHS that it is important to ensure that FDA's regulatory letters are legally supportable. As FDA agreed in its response to our 2002 report, however, it is also important for letters to be issued quickly. We believe that it is important for letters to be issued in a timely manner if they are to have an impact on halting the dissemination of the violative materials that the letters cite and reducing consumers' exposure to false or misleading advertising.

Background

The practice of advertising prescription drugs to consumers has been controversial. The United States is one of only two nations that allow DTC advertising (the other is New Zealand). In the United States, there have been concerns about the impact of DTC advertising on prescription drug spending and about potential safety issues, particularly with regard to the advertising of new drugs. These concerns have led to calls to restrict DTC advertising. For example, the Institute of Medicine recently recommended that DTC advertising be restricted during the first two years a new drug is marketed because some of the health risks of new drugs are not fully understood.¹¹

FDA regulates the content of all prescription drug advertising, whether directed to consumers or medical professionals. Advertising that is targeted to consumers includes both DTC and "consumer-directed" materials. DTC advertising includes, for example, broadcast advertisements (such as those on television and radio), print advertisements (such as those in magazines and newspapers), and Internet advertisements (such as consumer advertising on drug companies' Web sites).¹² In contrast, consumer-directed advertisements are designed to be

¹¹Institute of Medicine, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Washington, D.C.: The National Academies Press, September 2006).

¹²A drug company Web site may contain advertising directed to consumers, advertising directed to medical professionals, and product labeling.

given by medical professionals to consumers and include, for example, patient brochures provided in doctors' offices.

FDA requires that drug companies submit all final prescription drug advertising materials to the agency when they are first disseminated to the public.¹³ Drug companies are generally not required to submit advertising materials to FDA before they are disseminated.¹⁴ However, drug companies sometimes voluntarily submit draft DTC advertising materials to FDA in order to obtain advisory comments from the agency.¹⁵

Advertising materials must contain a "true statement" of information including a brief summary of side effects, contraindications, and the effectiveness of the drug.¹⁶ To meet this requirement, advertising materials must not be false or misleading, must present a fair balance of the risks and benefits of the drug, and must present any facts that are material to the use of the drug or claims made in the advertising. With the exception of broadcast advertisements, materials must present all of the risks described in the drug's approved labeling. Broadcast materials may present only the major side effects and contraindications, provided the

¹³21 C.F.R. § 314.81(b)(3)(2006).

¹⁴See 21 U.S.C. § 352(n)(3)(A) (providing that FDA generally may not require advertisements to be submitted for approval prior to dissemination). Advertising and promotional materials must be submitted to FDA before they are disseminated for drugs approved under FDA's accelerated approval process, which is for drugs that treat serious or life-threatening illnesses, and for drugs approved based on animal studies where human efficacy studies are not ethical or feasible. 21 C.F.R. §§ 314.550, 314.640(2006).

¹⁵PhRMA issued guidance effective January 2006 that states that "[drug] companies should submit all new DTC television advertisements to the FDA before releasing these advertisements for broadcast." PhRMA, *PhRMA Guiding Principles: Direct to Consumer Advertisements about Prescription Medicines* (Washington, D.C.: PhRMA, November 2005), <http://www.phrma.org/files/DTCGuidingprinciples.pdf> (last accessed July 31, 2006).

¹⁶21 C.F.R. § 202.1(e)(1)(2006). Those advertising materials that call attention to the name of the drug but do not include indication or dosage recommendations for use of the drug are exempt from these brief summary requirements.

materials make “adequate provision” to give consumers access to the information in the drug’s approved or permitted package labeling.¹⁷

Within FDA, DDMAC is responsible for implementing the laws and regulations that apply to prescription drug advertising. The division, which had 41 staff as of July 2006, is responsible for the oversight of both advertising directed to consumers and advertising directed to medical professionals. In March 2002, DDMAC created a DTC Review Group, which is responsible for oversight of advertising materials that are directed to consumers. Four Professional Review groups are responsible for oversight of promotional materials targeted to medical professionals. The DTC Review Group was allocated a group leader, four reviewers, and two social scientists when it was created. This group’s responsibilities include reviewing final DTC materials and reviewing and providing advisory comments on draft DTC materials. The group also monitors television, magazines, and consumer advertising on drug companies’ Web sites to identify advertising materials that were not submitted to FDA at the time they were first disseminated and reviews advertising materials cited in complaints submitted by competitors, consumers, and others. The two social scientists support reviewers in both the DTC and professional groups in their assessment of the content of advertising materials and conduct research related to DTC advertising, such as surveys of consumer and physician attitudes toward DTC advertising.

Once submitted to FDA, final and draft DTC advertising materials are distributed to a reviewer in the DTC Review Group. For final materials, if the reviewer identifies a concern, the agency determines whether it represents a violation and merits a regulatory letter. For draft materials submitted by drug companies, FDA may provide the drug company with advisory comments to consider before the materials are disseminated to

¹⁷FDA published draft guidance for DTC broadcast advertisements in 1997, and final guidance in 1999, that described an approach drug companies could use to meet the regulatory requirement for making adequate provision of key information. The outlined approach provides that drug companies disseminate complete information included in a drug’s approved package labeling through four alternative sources—including a toll-free number and a drug company Web site. See FDA, *Guidance for Industry: Consumer-Directed Broadcast Advertisements* (Rockville, Md.: FDA, August 1999). For other guidance related to DTC advertising, see FDA, *Draft Guidance for Industry: Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements* (Rockville, Md.: FDA, January 2004), and FDA, *Draft Guidance for Industry: Help-Seeking and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms* (Rockville, Md.: FDA, January 2004).

consumers if, for example, the reviewers identify claims in materials that could violate applicable laws and regulations.¹⁸

If FDA identifies violations in disseminated DTC materials, the agency can issue two types of regulatory letters—either a “warning letter” or an “untitled letter.” Warning letters are typically issued for violations that may lead FDA to pursue enforcement action if not corrected; untitled letters are issued for violations that do not meet this threshold. FDA generally posts issued letters on its Web site within several days of issuance.¹⁹ Both types of letters—which ranged from 2 to 9 pages, from 1997 through 2005—cite the type of violation identified in the company’s advertising material, request that the company submit a written response to FDA within 14 days, and request that the company take specific actions. Untitled letters request that companies stop disseminating the cited advertising materials and other advertising materials with the same or similar claims. In addition, warning letters further request that the company issue advertising materials to correct the misleading impressions left by the violative advertising materials. While FDA does not have explicit authority to require companies to act upon these letters, if the companies continue to violate applicable laws or regulations, the agency has other administrative and judicial enforcement avenues that could encourage compliance or result in the product being taken off the market. For example, FDA, through the Department of Justice, may seek additional remedies in the courts resulting in the seizure of drugs deemed to be misbranded because their advertising is false or misleading.

As reviewers from the DTC Review Group draft the regulatory letters, they sometimes obtain consultations from other FDA experts. For example, they may consult with the social scientists in the DTC Review Group about how consumers might interpret the violative materials, with the regulatory counsel in DDMAC about regulatory issues, or with a medical officer in FDA’s Office of New Drugs who has knowledge of a drug’s clinical testing and approval history. The reviewers may also consult with reviewers in DDMAC’s Professional Review groups.

¹⁸If FDA notifies the drug company that a draft material is not in violation and, at some subsequent time, changes its opinion, the agency is to notify the drug company in writing and is to provide it with a reasonable amount of time for correction before any regulatory action is taken. 21 C.F.R. § 202.1(j)(4)(2006).

¹⁹FDA, Center for Drug Evaluation and Research, *Warning Letters and Notice of Violation Letters to Pharmaceutical Companies* (Rockville, Md.: FDA, 2006), <http://www.fda.gov/cder/warn/> (last accessed Sept. 26, 2006).

Drug Company Spending on DTC Advertising Has Increased More Rapidly Than Spending on Promotion to Physicians or Research and Development

The draft regulatory letters are subsequently reviewed by officials in DDMAC, FDA's Office of Medical Policy (which oversees DDMAC), and OCC. In January 2002, at the direction of the Deputy Secretary of HHS, FDA implemented a policy change requiring OCC to review and approve all regulatory letters prior to their issuance, including letters drafted by the DTC Review Group, to ensure "legal sufficiency and consistency with agency policy."²⁰ In its written comments on a draft of our 2002 report, FDA stated that, prior to the policy change, there had been complaints that FDA would not follow up on many of its regulatory letters, and that the goal of the policy change was to promote voluntary compliance by ensuring that drug companies who receive a regulatory letter understand that the letter has undergone legal review and the agency is prepared to go to court if necessary.²¹

The amount that drug companies spend on DTC advertising increased twice as fast as spending on promotion to physicians or on research and development. IMS Health estimated that, from 1997 through 2005, spending on DTC advertising in the United States increased from \$1.1 billion to \$4.2 billion—an average annual increase of almost 20 percent.²² In contrast, over the same time period, IMS Health estimated that spending on drug promotion to physicians increased by 9 percent annually. Further, PhRMA reported that spending on the research and development of new drugs increased by about 9 percent annually during the same period.²³ While spending on DTC advertising has grown rapidly, companies continue to spend more on promotion to physicians and on research and development. In addition, IMS Health reports that the retail value of the free drug samples that companies provide to medical

²⁰Prior to the January 2002 policy change, OCC review and approval of draft regulatory letters before their issuance was not required. DDMAC officials told us, however, that prior to the policy change they routinely obtained feedback from OCC on draft warning letters.

²¹[GAO-03-177](#), p. 32.

²²IMS Health Inc., "Total U.S. Promotional Spend, by Type," *Top-Line Industry Data* (Fairfield, Conn.: IMS Health Inc., 2006), <http://www.imshealth.com/> (last accessed Aug. 21, 2006).

²³PhRMA, *Pharmaceutical Industry Profile 2006* (Washington, D.C.: PhRMA, March 2006).

professionals to distribute to their patients has increased by about 15 percent annually.²⁴ (See table 1.)

Table 1: Prescription Drug Promotion and Research and Development, 1997 through 2005

Dollars in billions

	1997	1998	1999	2000	2001	2002	2003	2004	2005	Average annual percentage increase	Total percentage increase, 1997-2005
Promotion											
Spending on DTC advertising ^a	\$1.1	\$1.3	\$1.8	\$2.5	\$2.7	\$2.6	\$3.3	\$4.0	\$4.2	19.6	296.4
Spending on promotion to physicians ^b	3.9	4.6	4.8	5.6	5.9	6.6	7.4	7.8	7.2	9.0	86.0
Retail value of samples ^c	6.0	6.6	7.2	8.5	10.5	11.9	13.5	15.9	n.a.	14.9 ^d	162.4 ^d
Research and Development											
Spending on research and development ^e	15.5	17.1	18.5	21.4	23.5	25.7	27.1	29.6	31.4 ^f	9.3	103.3

Sources: GAO analysis of IMS Health and PhRMA data.

Legend: n.a. = not available.

^aIncludes estimated spending on DTC advertising on television, in magazines and newspapers, on radio, and outdoors (such as on billboards). The estimates do not include other spending, such as spending to develop and maintain drug companies' Web sites or spending on sponsorship of sporting events.

^bIncludes estimated spending on office- and hospital-based promotion to physicians and journal advertising. These estimates do not include other spending, such as drug company spending on meetings and events, or spending on promotion that targets medical professionals other than physicians, such as nurse practitioners and physicians assistants.

^cWe used the retail value of drug samples as a measure of the volume of drug samples provided to physicians, but the retail value of samples does not directly reflect the amount spent by drug companies to manufacture and provide these samples.

^dRepresents data from 1997 through 2004.

^eIncludes spending on research and development reported by PhRMA member companies, as reported in PhRMA's annual industry review. Although not all drug companies are members of PhRMA, its member companies account for almost all spending on prescription drug promotion.

^fThis figure represents an estimate by PhRMA of spending for this year.

²⁴We used the retail value of drug samples as a measure of the volume of drug samples provided to physicians, but the retail value of samples does not directly reflect the amount spent by drug companies to manufacture and provide these samples.

Some types of promotional spending are not captured in the data we report. For example, figures for spending on DTC advertising do not include spending to develop and maintain drug companies' Web sites or spending on sponsorship of sporting events. In addition, some spending on promotion to medical professionals is not captured. For example, the data do not include drug company spending on meetings and events, or spending on promotion that targets medical professionals other than physicians, such as nurse practitioners and physicians assistants.

Drug companies concentrate their spending on DTC advertising in specific forms of media and on relatively few drugs. Television and magazine advertising represented about 94 percent of all spending on DTC advertising in 2005. DTC advertising also tends to be concentrated on relatively few brand name prescription drugs—in 2005, the top 20 DTC advertised drugs accounted for more than 50 percent of all spending on DTC advertising.²⁵ Many of the drugs most heavily advertised to consumers in 2005 were for the treatment of chronic conditions, such as high cholesterol, asthma, and allergies. Several of the drugs that have high levels of DTC advertising are also often promoted to physicians, and the drug companies often provide physicians with free samples of these drugs to be given to consumers.

Research Suggests DTC Advertising Increases Drug Spending and Utilization

Studies we reviewed suggest that DTC advertising increases prescription drug spending and utilization. It increases utilization by prompting some consumers to request the drugs from their physicians and for some physicians to prescribe the requested drugs. Evidence about increased utilization prompted by DTC advertising suggests it can have both positive and negative effects on consumers.

Studies we reviewed suggest that DTC advertising can increase drug spending for both the advertised drug and for other drugs that are used to treat the same condition. Studies have found that, for many drugs, DTC advertising increases sales of the drug itself, though the amount varies substantially. Across the studies we examined, estimates for certain drugs range from little change in sales to an increase of more than \$6 for every \$1 spent to advertise the specific drug. For example, one study of 64 drugs found a median increase in sales of \$2.20 for every \$1 spent on DTC

²⁵Med Ad News staff, "DTC Takes a Back Seat," *Med Ad News*, vol. 25, no. 5 (May 2006).

advertising.²⁶ The impact of DTC advertising on the sales of an individual drug depends on many factors. For example, one study found that, for the 63 drugs with the largest revenues in 2000, DTC advertising for newer drugs—launched in 1998 or 1999—increased sales more than DTC advertising for drugs launched from 1994 through 1997.²⁷ Further, research suggests that the sales of a specific drug may be affected by DTC advertising for other drugs that treat the same condition. For example, one study found that every \$1,000 spent on advertising for allergy drugs was associated with 24 new prescriptions for one specific allergy drug.²⁸

The studies we reviewed also suggest that DTC advertising increases prescribing by prompting some consumers to request the drugs from their physicians, and that physicians are generally responsive to the patient requests. Across the consumer and physician surveys that we reviewed,²⁹ about 90 percent of consumers report having seen a DTC advertisement. Studies have found that about 30 percent (ranging from 18 to 44 percent)

²⁶David Gascoigne and John Busbice for IMS, *DTC ROI: The Latest Findings* (presented at the DTC National Conference, Washington, D.C., Apr. 26, 2006).

²⁷Dick Wittink, *Analysis of ROI for Pharmaceutical Promotion (ARPP)* (Westfield, N.J.: The Association of Medical Publications, Inc., September 2002), http://www.rxpromoroi.org/arpp/media/arpp9_18dwittink.ppt (accessed May 19, 2006).

²⁸Woodie M. Zachry III et al., "Relationship between Direct-to-Consumer Advertising and Physician Diagnosing and Prescribing," *American Journal of Health-Systems Pharmacy*, vol. 59, no. 1 (2002).

²⁹Because the precise questions each survey asked and the resulting responses varied, we present general findings along with the relevant range of responses. The studies surveyed U.S. adults, but were not always representative of the general U.S. population. The surveys of consumer and physician behaviors that we reviewed included Prevention Magazine's *Eighth Annual Survey of Consumer Reaction to Direct-to-Consumer Advertising of Prescription Medicines* (Emmaus, Pa.: Prevention Magazine, 2005); Kathryn J. Aikin, John L. Swasy, and Amie C. Braman, *Patient and Physician Attitudes and Behaviors Associated With DTC Promotion of Prescription Drugs—Summary of FDA Survey Research Results* (Rockville, Md.: FDA, Nov. 19, 2004); Barbara Mintzes et al., "How Does Direct-to-Consumer Advertising (DTCA) Affect Prescribing? A Survey in Primary Care Environments with and without Legal DTCA," *Canadian Medical Association Journal*, vol. 169, no. 5 (2003); Sharon Allison-Otley, Karen Ruffin, and Kimberly Allison, "Assessing the Impact of Direct-to-Consumer Advertisements on the AA Patient: A Multisite Survey of Patients During the Office Visit," *Journal of the National Medical Association*, vol. 95, no. 2 (2003); Balaji Datti and Mary W. Carter, "The Effect of Direct-to-Consumer Advertising on Prescription Drug Use by Older Adults," *Drugs & Aging*, vol. 23, no. 1 (2006); Stephen E. Everett, "Lay Audience Response to Prescription Drug Advertising," *Journal of Advertising Research*, vol. 31, no. 2 (1991); The NewsHour with Jim Lehrer/Kaiser Family Foundation/Harvard School of Public Health, "National Survey on Prescription Drugs," (Menlo Park, Calif.: Kaiser Family Foundation, Sept. 2000), http://www.pbs.org/newshour/health/prescriptions/full_survey.pdf (accessed May 25, 2006).

of consumers who have seen DTC advertising reported discussing with their physician either the condition seen in an advertisement or an advertised drug. Of consumers who reported discussing an advertised condition or drug, about one quarter (ranging from 7 to 35 percent) reported requesting a prescription for the advertised drug. Surveys have found that of consumers who requested a drug they saw advertised, generally more than half (ranging from 21 to 84 percent) reported receiving a prescription for the requested drug. The surveys we reviewed found that between 2 and 7 percent of consumers who see a DTC advertisement requested and ultimately received a prescription for the advertised drug. Studies suggest that physicians are generally responsive to consumers' requests, and that decisions to prescribe a drug are influenced by a variety of factors in addition to a patient's medical condition. For example, studies have found that advertising in medical journals and visits from drug sales representatives may influence physician prescribing to a greater degree than DTC advertising.

Studies about DTC advertising and the increased utilization of prescription drugs it can prompt suggest that its effect on consumers can be both positive and negative. Some research suggests that DTC advertising can have benefits for consumers, such as encouraging them to talk to their doctors about previously undiagnosed conditions. For example, one study found that DTC advertising is associated with the diagnosis and treatment of high cholesterol with prescription drugs.³⁰ Similarly, another study found that DTC advertising for antidepressant drugs was associated with an increase in the number of people diagnosed with depression and who initiated drug therapy, as well as with a small increase in patients who received the appropriate duration of therapy.³¹ In contrast, other research suggests that DTC advertising can have negative effects, such as encouraging increases in prescriptions for advertised drugs when alternatives may be more appropriate. For example, one study found that consumers who requested a pain medication as a result of DTC advertising were more likely to get the requested drug than a drug more appropriate

³⁰Woodie M. Zachry III et al., "Relationship between Direct-to-Consumer Advertising and Physician Diagnosing and Prescribing."

³¹Julie M. Donohue et al., "Effects of Pharmaceutical Promotion on Adherence to the Treatment Guidelines for Depression," *Medical Care*, vol. 42, no. 12 (2004).

for those consumers.³² Another study, using actors posing as patients, found that 55 percent of those who presented with symptoms of adjustment disorder and requested a specific antidepressant received an antidepressant, even though treatment with drugs may not have been appropriate given their symptoms.³³

FDA Reviews a Small Portion of DTC Materials and Cannot Ensure It Is Reviewing the Highest-Priority Materials

FDA reviews a small portion of the increasingly large number of DTC materials it receives. FDA attempts to target available resources by focusing its reviews on the DTC advertising materials that have the greatest potential to impact public health, but the agency has not documented criteria for prioritizing the materials it receives for review. FDA officials told us that agency reviewers consider several informal criteria when prioritizing the materials. However, FDA does not apply these criteria systematically to the materials it receives. Instead, FDA relies on each of the reviewers to be aware of the materials the agency has received and accurately apply the criteria to determine the specific materials to review. Further, the agency does not document if a particular DTC material was reviewed. As a result, the agency cannot ensure that it is identifying or reviewing the materials that are the highest priority.

FDA Reviews a Small Portion of DTC Advertising Materials

FDA reviews a small portion of the increasingly large number of DTC materials submitted to the agency by drug companies. In 2005, FDA received 4,600 final DTC materials (excluding Internet materials) and 6,168 final Internet materials.³⁴ FDA also received 4,690 final consumer-directed materials—such as brochures given to consumers by medical professionals. As shown in figure 1, FDA has received a steadily increasing

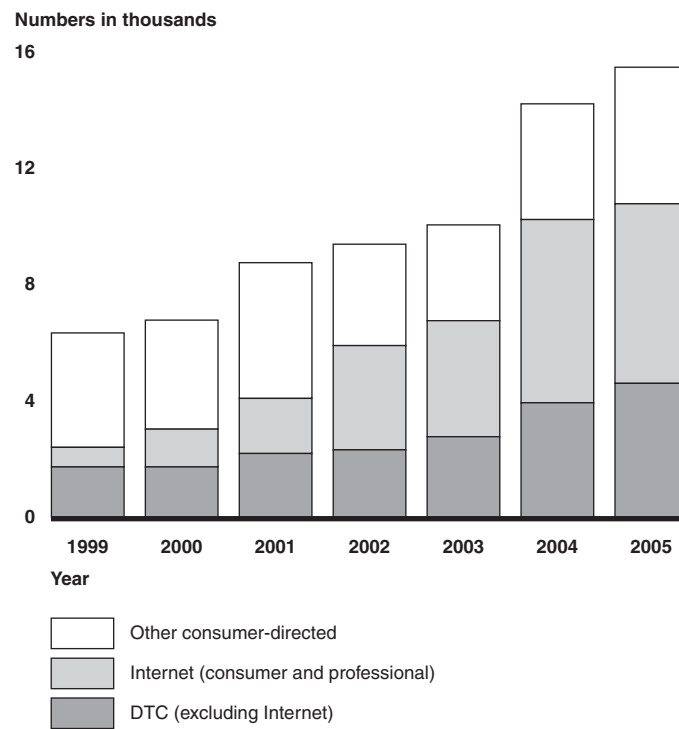
³²Michele M. Spence et al. "Direct-to-Consumer Advertising of COX-2 Inhibitors: Effect on Appropriateness of Prescribing," *Medical Care Research and Review*, vol. 62, no. 5 (2005). This study evaluated the appropriateness of a prescription by determining whether it was consistent with a patient's risk of gastrointestinal bleeding, which was assessed according to three evidence-based risk assessment guidelines.

³³Richard L. Kravitz et al., "Influence of Patients' Requests for Direct-to-Consumer Advertised Antidepressants," *Journal of the American Medical Association*, vol. 293, no. 16 (2005). This study used actors trained to present a standard set of symptoms to office-based physicians and to make standard requests for treatment in accordance with the established study protocol.

³⁴We present Internet materials separately from other DTC materials because FDA's count of submitted materials does not distinguish between Internet materials targeted to consumers and those targeted to medical professionals. However, FDA officials told us that most Internet materials, such as drug companies' Web sites, include both a consumer and a professional component.

number of final materials from 1999 through 2005. We could not determine whether there has been a similar increase in the number of draft DTC materials FDA has received because the agency does not track this information.³⁵

Figure 1: Number of Final DTC and Consumer-Directed Materials Submitted to FDA, 1999 through 2005



Source: GAO analysis of FDA data.

Notes: We do not include final DTC materials submitted to FDA in 1997 and 1998 because FDA changed the way it categorized submitted materials in 1999. We present Internet materials separately from DTC materials because FDA's data do not distinguish between Internet materials that are targeted to consumers and those targeted to professionals. However, FDA officials told us that most Internet materials contain a consumer component.

³⁵FDA tracks the number of submissions of draft DTC materials, rather than the actual number of draft materials. These submissions can include both materials directed to consumers and materials targeted to medical professionals, and FDA officials estimated that each submission could contain as few as 1 or as many as 60 separate draft materials. As a result, we were unable to determine the number of draft DTC materials submitted to FDA in a given year.

FDA officials told us that the agency receives substantially more final and draft materials than the DTC Review Group can review. The total number of final materials has almost doubled since FDA formed its DTC Review Group in March 2002. FDA officials told us that the group was not fully staffed until September 2003 and that turnover has been a problem, temporarily reducing the number of reviewers in the group from four to one in late summer 2005. FDA has since filled all of the positions in the group and it added a fifth reviewer in September 2006.³⁶ Officials told us that it can take 6 months to a year for new reviewers to become fully productive.

FDA officials estimate that reviewers spend the majority of their time reviewing and commenting on draft materials. However, we were unable to determine the number of final or draft materials FDA reviews, because FDA does not track this information. In the case of final and draft broadcast materials, FDA officials told us that the DTC group reviews all of the materials it receives; in 2005, it received 337 final and 146 draft broadcast materials. However, FDA does not document whether these or other materials it receives have been reviewed. As a result, FDA cannot determine how many materials it reviews in a given year.

FDA Cannot Ensure That It Is Reviewing the Highest-Priority DTC Advertising Materials

FDA cannot ensure that it is identifying and reviewing the highest-priority DTC materials because it does not have documented criteria that it systematically uses to select DTC materials for review. FDA officials told us that, to target available resources, the agency prioritizes the review of the DTC advertising materials that have the greatest potential to impact public health. However, FDA has not documented criteria for reviewers in the DTC Review Group to consider when prioritizing materials for review. Instead, FDA officials identified informal criteria that reviewers use to prioritize their reviews. For example, FDA officials told us that the DTC Review Group reviews all final and draft broadcast DTC advertising materials because they are likely to be disseminated to a large number of people. In addition, FDA officials told us that the agency places a high priority on reviewing other draft materials because they provide the agency with an opportunity to identify problems and ask drug companies

³⁶FDA officials told us that DDMAC has been approved to hire two additional full-time employees, whom DDMAC plans to hire for the DTC Review Group.

to correct them before the materials are disseminated to consumers.³⁷ In addition, FDA officials told us that reviewers consider whether

- a nonbroadcast material is likely to be widely disseminated to consumers;
- a drug has been cited in previous regulatory letters;
- a drug is being advertised to consumers for the first time;
- a drug is one of several drugs that can be used to treat the same condition, which FDA believes increases the likelihood that advertising will use comparative claims that may not be supported by available scientific evidence;
- a drug is cited in a complaint submitted by a competitor, consumer, or other stakeholder;
- a drug has had recent labeling changes, such as the addition of new risk information; or
- a drug was approved under FDA's accelerated approval process.

FDA officials indicated that the agency does not systematically apply its informal criteria to all of the materials that it receives. Specifically, at the time FDA receives the materials, the agency does not identify the materials that meet its various criteria. FDA officials told us that the agency does identify all final and draft broadcast materials that it receives, but does not have a system for identifying any other high-priority materials. Absent such a system for all materials, FDA relies on each of the reviewers—in consultation with other DDMAC officials—to be aware of the materials that have been submitted and to accurately apply the criteria to determine the specific materials to review. This creates the potential for reviewers to miss materials that the agency would consider to be a high priority for review. Furthermore, because FDA does not track information on its reviews, the agency cannot determine whether a particular material has been reviewed. As a result, the agency cannot ensure that it is identifying and reviewing the highest-priority materials.

³⁷We did not examine the effectiveness of FDA's review of draft materials in preventing the dissemination of violative DTC materials because FDA does not track whether the draft materials it reviews are later cited in a regulatory letter.

Since the 2002 Policy Change, FDA's Process for Issuing Regulatory Letters Has Taken Longer and the Agency Has Issued Fewer Letters

Since the 2002 policy change requiring legal review by OCC of all draft regulatory letters, the agency's process for drafting and issuing letters has taken longer and FDA has issued fewer regulatory letters per year. As a result of the policy change, draft regulatory letters receive additional levels of review and the DTC reviewers who draft the letters must do substantially more work to prepare for and respond to comments resulting from review by OCC. Since the policy change, FDA has issued fewer regulatory letters per year than it did in any year prior to the change. FDA officials told us that the agency issues letters for only the violative DTC materials that it considers the most serious and most likely to impact consumers' health.

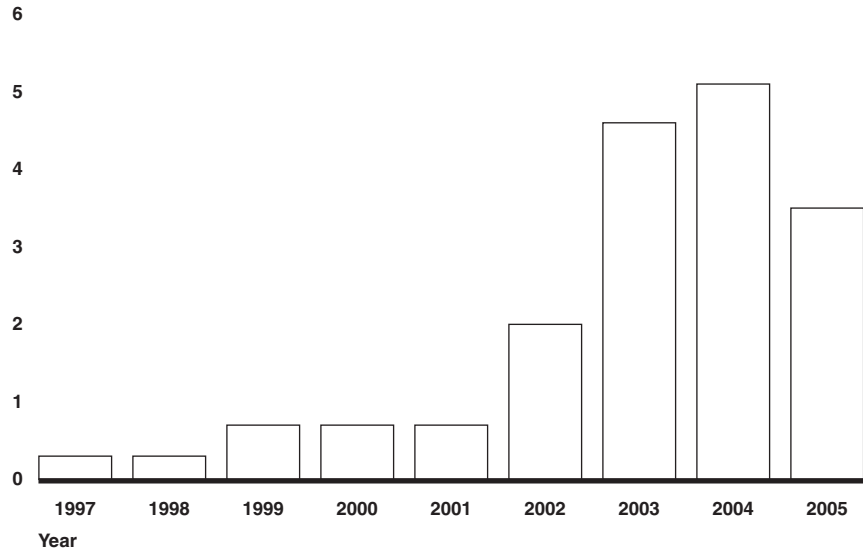
FDA's Process for Issuing Regulatory Letters Has Taken Longer Since the 2002 Policy Change

Since the 2002 policy change requiring legal review of all draft regulatory letters, FDA's process for issuing letters has taken longer. Once FDA identifies a violation in a DTC advertising material and determines that it merits a regulatory letter, FDA takes several months to draft and issue a letter.³⁸ (See fig. 2.) For letters issued from 2002 through 2005, once DDMAC began drafting a letter for violative DTC materials it took an average of about 4 months to issue the letter. The length of this process varied substantially across these regulatory letters—one letter took around 3 weeks from drafting to issuance, while another took almost 19 months. In comparison, for regulatory letters issued from 1997 through 2001, it took an average of 2 weeks from drafting to issuance. During this earlier time period, 11 letters were issued the day they were drafted, and the longest time from drafting to issuance was slightly more than 6 months.

³⁸FDA does not track when it identifies a violation in a DTC material and determines that it merits a regulatory letter. Because the agency does, however, document the date on which reviewers first began drafting a letter, we examined the amount of time it took for FDA to draft and issue a letter.

Figure 2: Average Months to Issue Regulatory Letters Citing Violative DTC Materials, 1997 through 2005

Months to issue regulatory letters (initial draft to issuance)



Source: GAO analysis of FDA documents.

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

The primary factor contributing to the increase in the length of FDA's process for issuing regulatory letters is the additional work that resulted from the 2002 policy change. In addition to the time required of OCC, DDMAC officials told us that the policy change has created the need for substantially more work on their part to prepare the necessary documentation for legal review. According to DDMAC officials, to prepare for initial meetings with OCC on draft regulatory letters reviewers prepare extensive background information describing the violations as well as the drug and its promotional history. As a part of this process, DDMAC reviewers sometimes seek consultations with regulatory and clinical experts within FDA. For example, reviewers may request consultations with the medical officers in FDA's Office of New Drugs in order to determine whether available data from the drug approval process are

sufficient to support the advertising claims being made in DTC materials.³⁹ After incorporating comments from the requested consultations, DDMAC reviewers hold their initial meeting with OCC and subsequently revise the draft regulatory letter to reflect the comments from OCC. Once these initial revisions are complete, DDMAC formally submits a draft regulatory letter to OCC for legal review and approval. All DDMAC regulatory letters are reviewed by both OCC staff and OCC's Chief Counsel. OCC often requires additional revisions to the draft regulatory letter before OCC will concur that a letter is legally supportable and can be issued. Depending on comments provided by OCC, the DDMAC reviewers may request additional consultations with FDA experts at each stage of review.

OCC officials told us that the office has given regulatory letters that cite violative DTC materials higher priority than other types of regulatory letters, but that the attorneys have many other responsibilities. Prior to 2005, OCC had two staff attorneys and one supervising attorney assigned to review all of the regulatory letters submitted by DDMAC, including the letters that cite DTC materials. However, OCC officials told us that the review of DDMAC's draft regulatory letters is a small portion of their total responsibilities and must be balanced with other requests, such as the examination of legal issues surrounding the approval of a new drug. OCC officials told us that, in 2005, the office assigned two additional attorneys in an attempt to help issue the DDMAC regulatory letters more quickly.

Prior to September 2005, OCC had a goal of providing initial comments to DDMAC within 15 business days from the date that a letter citing DTC materials was formally submitted.⁴⁰ Based on our review of DDMAC's and OCC's documentation for the 19 letters issued from 2004 through 2005, we

³⁹Of the 19 regulatory letters FDA issued from 2004 through 2005, reviewers obtained a consultation from the social scientists in the DTC Review Group for 5 letters and from medical officers in the Office of New Drugs for 9 letters. FDA officials told us that some of these consultations were due to increasingly complex advertising claims—for example, claims that the drug is more effective than other drugs—and DTC advertising for more complex drugs—for example, drugs that treat the human immunodeficiency virus or diabetes. We did not examine the numbers of consultations obtained in prior years because FDA officials told us that its documentation of consultations in earlier years was not reliable.

⁴⁰OCC officials indicated that OCC changed this goal in September 2005 and now has a goal of providing initial comments to DDMAC within 10 business days from the date that a letter is formally submitted. We used the 15-day goal in our analysis because each of the 19 regulatory letters issued from 2004 through 2005 were submitted to OCC prior to September 2005.

estimated that OCC generally met its 15-day goal for providing initial comments. However, the goal OCC established is not directly relevant to the total amount of time it takes FDA to issue the regulatory letter once it has been formally submitted to OCC because DDMAC must make changes to the letters to respond to OCC's comments and OCC may review letters more than once. For regulatory letters issued from 2004 through 2005 that cited violative DTC materials, we found that, once DDMAC had formally submitted a draft letter to OCC, it took an average of about 3 months for the letter to receive final OCC concurrence and be issued. FDA does not have a goal for how long it should take the agency to issue a letter from the time that OCC first formally receives a draft of the letter.⁴¹

FDA Issued Fewer Regulatory Letters Citing Violative DTC Advertising Materials after Its 2002 Policy Change

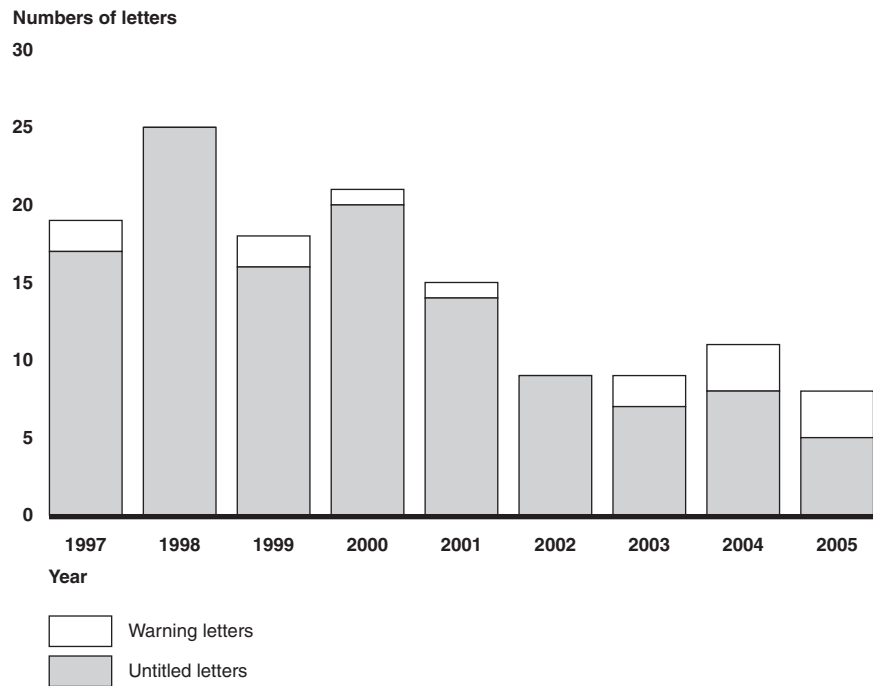
The number of regulatory letters FDA issued per year for violative DTC materials decreased after the 2002 policy change lengthened the agency's process for issuing letters. From 2002 to 2005, the agency issued between 8 and 11 regulatory letters per year that cited DTC materials.⁴² (See fig. 3.) Prior to the policy change, the agency issued about twice as many such regulatory letters per year. From 1997 through 2001, FDA issued between 15 and 25 letters citing DTC materials per year. An FDA official told us that both the lengthened review time resulting from the 2002 policy change and staff turnover within the DTC Review Group contributed to the decline in the number of issued regulatory letters. In addition, from 2002 through 2005,⁴³ FDA did not ultimately issue 10 draft regulatory letters citing DTC materials that DDMAC had submitted to OCC for the required legal review. For 5 letters, OCC determined that there was insufficient legal support for issuing the letters and, therefore, did not concur with DDMAC. DDMAC withdrew the other 5 letters from OCC's consideration but could not provide us with information on why it withdrew these letters.

⁴¹HHS indicated in its written comments on a draft of our October 2002 report that it had "established a goal of issuing regulatory letters within 15 working days of review at OCC" (GAO-03-177, p. 33). However, FDA officials have subsequently told us that there is no set goal for issuing regulatory letters and, instead, OCC had agreed to provide DDMAC with initial comments within 15 business days from the date draft regulatory letters citing DTC materials were formally submitted to OCC.

⁴²From January through September 2006, FDA issued three regulatory letters citing violative DTC materials, one of which was a warning letter.

⁴³FDA officials indicated that OCC began tracking information on its reviews of draft regulatory letters in April 2002.

Figure 3: Number of Regulatory Letters FDA Issued That Cited DTC Advertising Materials, 1997 through 2005



Source: GAO analysis of FDA regulatory letters.

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

FDA regulatory letters may cite more than one DTC material or type of violation for a given drug.⁴⁴ Of the 19 regulatory letters FDA issued from 2004 through 2005, 7 cited more than 1 DTC material, for a total of 31

⁴⁴Of the 19 regulatory letters issued from 2004 through 2005, 18 cited violative advertising materials for only one drug. One letter cited materials for two drugs promoted by a single company.

different materials.⁴⁵ These 31 materials appeared in a range of media, including television, radio, print, direct mail, and Internet. Further, FDA identified multiple violations in 21 of the 31 DTC materials cited in the letters. The most commonly cited violations related to a failure of the material to accurately communicate information about the safety of the drug. For example, FDA wrote in 5 letters that distracting visuals in cited television advertisements minimized important information about the risk of the drug. The letters also often cited materials for overstating the effectiveness of the drug or using misleading comparative claims.

FDA Issues Regulatory Letters Only for DTC Advertising Materials It Considers Most Likely to Negatively Impact Consumers

FDA officials told us that the agency issues regulatory letters for DTC materials that it believes are the most likely to negatively impact consumers and does not act on all of the concerns that its reviewers identify. When reviewers have concerns about DTC materials, they discuss them with others in DDMAC and may meet with OCC and medical officers in FDA's Office of New Drugs to determine whether a regulatory letter is warranted or on the content of the letter itself. FDA officials told us that the agency issues regulatory letters only for the violative materials that it considers the most likely to negatively impact public health. For example, they said the agency may be more likely to issue a letter when a false or misleading material was broadly disseminated to a large number of consumers. In addition, FDA officials told us that they are more likely to issue a regulatory letter when the drug is one of several drugs that can be used to treat the same condition; they said that the issuance of a regulatory letter in this situation may enhance future voluntary compliance by promoters of the competing drugs. However, because FDA does not document decisions made at the various stages of its review process about whether to pursue a violation, officials were unable to provide us with an estimate of the number of materials about which concerns were raised but the agency did not issue a letter.

⁴⁵Of the 19 regulatory letters citing DTC materials, 2 also cited materials intended to be provided to consumers by medical professionals and 5 also cited materials targeted directly to medical professionals.

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

FDA regulatory letters have been limited in their effectiveness at halting the dissemination of false and misleading DTC advertising materials. We found that, from 2004 through 2005, FDA issued regulatory letters an average of about 8 months after the violative DTC materials they cited were first disseminated. By the time these letters were issued, drug companies had already discontinued more than half of the cited materials. For the materials that were still being disseminated, drug companies removed the cited materials in response to FDA's letter. Drug companies also identified and removed other materials with claims similar to the materials cited in the regulatory letters. Although drug companies complied with FDA's requests to create materials that correct the misimpressions left by the cited materials, these corrections were not disseminated until 5 months or more after FDA issued the regulatory letter. Despite halting the dissemination of both cited and other violative materials at the time the letter was issued, FDA's issuance of these letters did not always prevent drug companies from later disseminating similar violative materials for the same drugs.

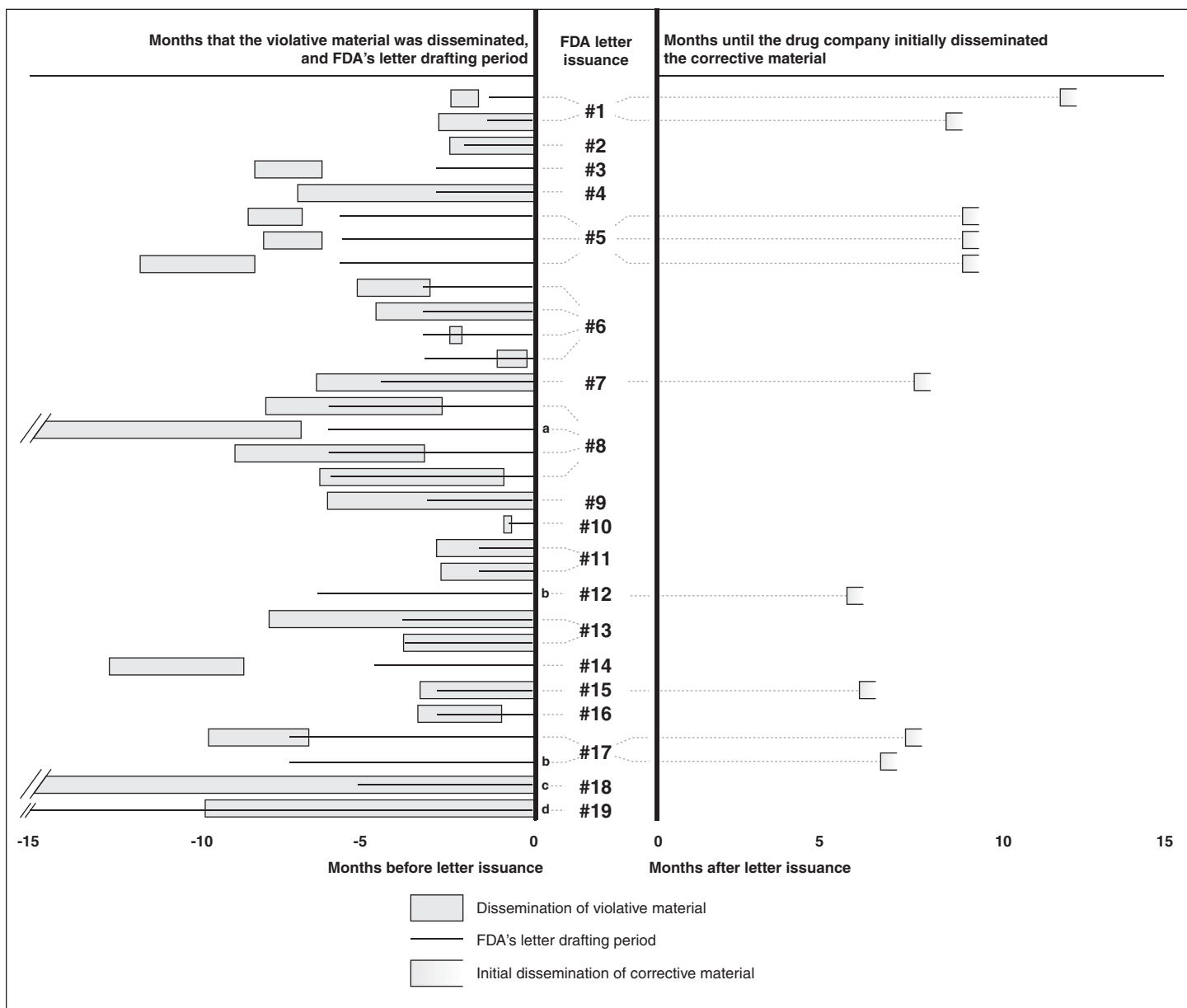
Lack of Timely Issuance of Regulatory Letters Limits FDA's Effectiveness at Halting Violative DTC Advertising Materials

FDA's regulatory letters have been limited in their effectiveness at halting the dissemination of the violative DTC materials they cite. Because of the length of time it took FDA to issue these letters, violative advertisements were often disseminated for several months before the letters were issued. From 2004 through 2005, FDA issued regulatory letters citing DTC materials an average of about 8 months after the violative materials were first disseminated. FDA issued one letter less than 1 month after the material was first disseminated, while another letter took over 3 years. The cited materials were usually disseminated for 3 or more months, though there was substantial variability across materials. Of the 31 violative DTC materials cited in these letters, 16 were no longer being disseminated by the time the letter was issued. On average, these letters were issued more than 4 months after the drug company stopped disseminating these materials, and therefore had no impact on their dissemination. For the 14 DTC materials that were still in use when FDA issued the letter, the drug companies complied with FDA's request to stop disseminating the violative materials.⁴⁶ However, by the time the letters were issued, these 14 materials had been disseminated for an average of about 7 months.⁴⁷ See figure 4 for information on the timeliness of the 19 regulatory letters relative to the dissemination of the DTC advertising materials they cited.

⁴⁶For one violative advertising material, we were unable to determine from FDA's case files when the violative advertising material ended.

⁴⁷This average is based on 12 of 14 advertising materials for which we were able to determine the length of time the materials were disseminated.

Figure 4: Timelines for 19 Regulatory Letters Issued from 2004 through 2005 and the Cited DTC Materials



Source: GAO analysis of FDA regulatory letters and documentation.

Note: Of these 19 regulatory letters, 18 cited violative advertising materials for a single drug. In one instance, the letter cited materials promoting two drugs promoted by a single company.

^aThe drug company started disseminating the violative DTC material about 36 months before FDA issued the regulatory letter.

^bWe were unable to determine from FDA's documentation the date the drug company first disseminated the violative material. However, the drug company indicated in correspondence with FDA that it stopped disseminating the material when it received the regulatory letter.

^cThe drug company started disseminating the violative material about 31 months before FDA issued the regulatory letter.

^dFDA started drafting the regulatory letter about 19 months before the letter was issued. This letter, which was drafted about 9 months before the violative DTC material was first disseminated, also cited materials directed to medical professionals, and those materials are not represented in this figure. In addition, we were unable to determine from FDA's documentation the date the drug company stopped disseminating the violative material. However, the drug company indicated that the material was no longer being disseminated when it initially responded to FDA's regulatory letter.

FDA Regulatory Letters Led Drug Companies to Identify and Remove Materials Similar to the Violative DTC Advertising Materials

As requested by FDA in the regulatory letters, drug companies often identified and stopped disseminating other materials with claims similar to those in the violative materials. For 18 of the 19 regulatory letters issued from 2004 through 2005, the drug companies indicated to FDA that they had either identified additional similar materials or that they were reviewing all materials to ensure compliance.⁴⁸ Some of these drug companies indicated in their correspondence with FDA which similar materials they had identified. Specifically, drug companies responding to 13 letters indicated that they had identified and stopped disseminating between 1 and 27 similar DTC and other materials directed to consumers that had not been cited in the regulatory letter. In addition to halting materials directed to consumers, companies responding to 11 letters also stopped disseminating materials with similar claims that were targeted directly to medical professionals.⁴⁹

Drug Companies Disseminated Corrective Advertising Materials 5 Months or More after FDA Issued the Regulatory Letter

Drug companies disseminated the corrective advertising materials requested in FDA warning letters, but took 5 months or more to do so. In each of the six warning letters FDA issued in 2004 and 2005 that cited DTC materials, the agency asked the drug company to disseminate truthful, nonmisleading, and complete corrective messages about the issues discussed in the regulatory letter to the audiences that received the violative promotional materials. In each case, the drug company complied with this request by disseminating corrective advertising materials. For four warning letters we were able to examine the resulting corrective

⁴⁸For one letter, the FDA documentation we reviewed did not contain the drug company's written response.

⁴⁹In their responses, the drug companies identified between 1 and 18 materials directed to medical professionals.

materials and found that they each contained an explicit reference to the regulatory letter and a message intended to correct misleading impressions created by the violative claim.⁵⁰ In addition, the drug companies provided evidence to FDA that the materials would be disseminated to a consumer population similar to the one that received the original violative advertising materials. For example, one drug company provided FDA with the broadcast schedule for the violative television advertisement and the planned schedule for the corrective advertising material to demonstrate that it would run on similar channels, at similar times, and with similar frequency.

For the six warning letters FDA issued in 2004 and 2005 that cited DTC materials, the corrective advertising materials were initially disseminated more than 5 to almost 12 months after FDA issued the letter. For example, for one allergy medication, the violative advertisements ran from April through October 2004, FDA issued the regulatory letter in April 2005, and the corrective advertisement was not issued until January 2006. FDA officials told us that the process of issuing a corrective advertisement is lengthy because the agency and the drug company negotiate the content and format of the corrective advertisements. They also said that, in some cases, FDA reviewers work closely with the drug company to develop, and sometimes suggest specific content for, the corrective advertisement. See figure 4 for more detail on the dissemination of the corrective advertisements.

FDA Regulatory Letters Do Not Always Prevent Subsequent Dissemination of Violative DTC Materials for the Same Drug

FDA regulatory letters do not always prevent the same drug companies from later disseminating violative DTC materials for the same drug, sometimes using the same or similar claims. From 1997 through 2005, FDA issued regulatory letters for violative DTC materials used to promote 89 different drugs.⁵¹ Of these 89 drugs, 25 had DTC materials that FDA cited in more than one regulatory letter, and one drug had DTC materials cited in eight regulatory letters. For 15 of the 25 drugs, FDA cited similar broad

⁵⁰For two regulatory letters, the FDA documentation that we reviewed did not contain a copy of the corrective material that had been disseminated by the drug company.

⁵¹When multiple drugs contained the same active ingredient, we considered them to be the same drug for the purposes of this analysis. For example, we considered the tablet and syrup versions of a drug to be a single drug product because they contained the same active ingredient.

categories of violations in multiple regulatory letters.⁵² For example, FDA issued regulatory letters citing DTC materials for a particular drug in 2000 and again in 2005 for “overstating the effectiveness of the drug.” However, the specific claims cited in each of these regulatory letters differed. In 2000, FDA wrote in its regulatory letter that the “totality of the image, the music, and the audio statements” in a television advertisement overstated the effectiveness of the drug. The 2005 letter stated that a different television advertisement overstated effectiveness by suggesting that the drug was effective for “preventing or modifying the progression of arthritis” when the drug was approved for the “relief of the signs and symptoms” of arthritis. For 4 of the 15 drugs, FDA cited the same specific violative claim for the same drug in more than one regulatory letter. (See table 2.) For example, in 1999 FDA cited a DTC direct mail piece for failing to convey important information about the limitations of the studies used to approve the promoted drug. In 2001, FDA cited a DTC broadcast advertisement for the same drug for failing to include that same information.

⁵²We did not examine how many of the drugs that were cited for violative DTC materials had also been cited for violative materials directed to medical professionals. However, during our review of the regulatory letters, we noted that some drugs have had both types of materials cited, and that FDA sometimes cited the same or similar violative claims in both types of materials. In addition, the regulatory letters we reviewed sometimes stated that FDA, based on its review of draft versions of advertising materials, had previously issued advisory comment letters expressing its concern about drug companies’ use of the claims cited in the regulatory letter.

Table 2: Drugs for Which FDA Cited the Same Specific Violative Claim in More Than One Regulatory Letter

Drug product (company)	Condition	Material cited in FDA letter	
		First letter	Subsequent letter
Ditropan XL (Alza Corporation)	Overactive bladder	Letter cited a DTC direct mail letter for failing to convey that the clinical studies were set up to include only patients whom the company knows would have improved symptoms on Ditropan XL because they were known to have had improved symptoms on oxybutynin, the active ingredient in Ditropan XL, or other similar medications used to treat overactive bladder. (Apr. 2, 1999)	Letter cited a DTC broadcast advertisement and a DTC print advertisement for failing to prominently disclose important facts—specifically, that the clinical trials for Ditropan XL were set up to include only patients who were known to have had improved symptoms on oxybutynin, or other similar medications used to treat overactive bladder. (July 12, 2001)
		Letter cited a DTC direct mail letter for failing to disclose that patients randomized to the placebo arm experienced a 51% reduction in the number of wetting accidents. (Apr. 2, 1999)	Letter cited a DTC print advertisement for failing to prominently disclose that patients randomized to placebo experienced a 51% reduction in the number of wetting accidents. (July 12, 2001)
MUSE (VIVUS Inc.)	Erectile dysfunction	Letter cited a DTC print advertisement for not providing qualifying information with sufficient prominence to balance out the headline claim “Impotence is Optional.” (Feb. 19, 1998)	Letter cited a DTC print advertisement for not displaying a qualifying subhead with the prominence necessary to provide the context needed for the headline “Impotence is Optional.” (Apr. 1, 1998)
		Letter cited a DTC print advertisement for failing to communicate an important material characteristic of the drug because FDA considers the term “urethral suppository” to be an unfamiliar medical term for the average consumer that does not disclose how the drug is used. (Apr. 1, 1998)	Letter cited a DTC television advertisement for failing to adequately disclose how the drug is used; FDA’s letter specifically references the related citation from its April 1, 1998 letter. (May 25, 2004)
Nolvadex (AstraZeneca Pharmaceuticals LP)	Breast cancer	Letter cited a DTC direct mail advertisement for not providing adequate context for a risk reduction claim. Without additional context, the use of this claim overstates the efficacy of the drug at reducing incidence of breast cancer in women at high risk. (July 20, 2000)	Letter cited a DTC print advertisement for not providing adequate context for a risk reduction claim. Without additional context, the use of this claim overstates the efficacy of the drug at reducing occurrence of new cancers. (Dec. 14, 2001)
Prevacid (TAP Pharmaceutical Products Inc.)	Gastro-esophageal reflux disease	Letter cited a DTC television advertisement for not clearly communicating the indication, which implies that the drug may be used in a broader range of conditions because disclosed limitations to the indication are nonprominent, hard to comprehend, and displayed against distracting visual backgrounds. (Mar. 15, 2000)	Letter cited a DTC television advertisement for failing to clearly communicate limitations of the approved indication because communication of the indication is interfered with by competing visual, graphic, and auditory distractions that combine to interfere with, and undermine, a typical consumer’s reading and comprehension. (Aug. 2, 2002)

Source: GAO analysis of FDA regulatory letters.

Conclusions

Given substantial increases in drug company spending on DTC advertising in recent years, and evidence that DTC advertising can influence consumers' behavior, it is important to develop a full understanding of its impact on the U.S. health care system. It is also important that FDA effectively limit the dissemination of DTC advertising that is false or misleading. Because FDA reviews a small portion of the final and draft DTC materials that it receives, it is important that the agency have a process to identify and review the materials that are the highest priority. However, FDA lacks documented criteria for identifying and prioritizing DTC materials for review, a process to ensure that criteria are applied systematically to all materials received, and a system for tracking whether materials have been reviewed. As a result, FDA cannot be assured that the highest-priority materials have been identified or reviewed.

Given the length of time it takes FDA to issue regulatory letters and the potential for repeated use of violative claims, we are concerned about FDA's effectiveness at limiting consumers' exposure to false or misleading DTC advertising. In our 2002 report, we recommended that HHS take steps to reduce the time that FDA's DTC draft regulatory letters are under review. In its written response to the recommendation in that report, HHS agreed that it needs to issue DTC regulatory letters more quickly and established a goal of issuing the letters "within 15 working days of review at OCC." However, we have now found that it takes FDA months to complete the process of drafting and reviewing the letters. As we previously recommended, we believe that regulatory letters must be issued more quickly.

Recommendations for Executive Action

To improve FDA's processes for identifying and reviewing final and draft DTC advertising materials, we recommend that the Acting Commissioner of the Food and Drug Administration take the following three actions:

- document criteria for prioritizing materials that it receives for review,
- systematically apply its documented criteria to all of the materials it receives, and
- track which materials have been reviewed.

Agency Comments and Our Evaluation

HHS reviewed a draft of this report and provided comments, which are reprinted in appendix II.

In its comments, HHS generally agreed with our description of FDA's oversight of DTC advertising, but disagreed with our recommendations and some aspects of our conclusions. First, HHS disagreed with our recommendations that it systematically prioritize and track the DTC advertising materials it reviews. HHS stated that DDMAC now reviews all of some types of high priority DTC materials, especially final and draft broadcast advertisements. HHS also commented that, although DDMAC has not documented its selection criteria, those criteria are systematically applied by its reviewers to determine workload priorities. HHS also noted that reviewing each DTC material received according to selection criteria and tracking the reviews that DDMAC conducts would require DDMAC's staff to be vastly increased.

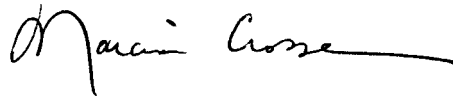
We recognize that, with current staffing, DDMAC's DTC Review Group cannot review in detail the more than 10,000 DTC materials that are submitted to the agency each year and that DDMAC now focuses its review efforts specifically on broadcast materials and draft materials. However, it is because DDMAC's reviewers are only able to review selected materials that we believe it is important for FDA to develop a more complete and systematic process for screening the materials the agency receives. To do so, the informal criteria that reviewers now consider when prioritizing reviews should be formalized to help ensure consistent application. Contrary to HHS's comments, we do not agree that systematically applying these criteria would require that every DTC material be reviewed in detail. Instead, FDA should apply the criteria as a screening mechanism to all materials it receives. Furthermore, FDA already has most of the information that would be necessary to establish a system to screen submitted materials against these criteria. For instance, when drug companies submit DTC materials to FDA, the agency records information about the drug being advertised and the type of material submitted. Additionally, for most of the priority criteria described in our report, FDA already has information—such as whether the drug has been the subject of a previous regulatory letter or a recent label change—needed to determine how the criteria would apply to materials used to promote a given drug.

Second, HHS also expressed concern that our draft report criticized the agency for the length of time it takes to issue regulatory letters and declines in the number of letters issued since the policy change requiring review by OCC, without adequately addressing the underlying purpose of that review. HHS commented that its policy change has led to more defensible regulatory letters and better compliance after issuance. We agree with HHS that it is important to ensure that FDA's regulatory letters are legally supportable, and, as HHS noted, we did not examine the effect of the policy change on the legal sufficiency of the letters in this report. However, we also believe that it is important for letters to be issued in a timely manner if they are to have an impact on halting the dissemination of the violative materials that the letters cite. In 2002, HHS agreed with the recommendation of our earlier report that DTC regulatory letters be issued more quickly. Nonetheless, as we noted in the draft of this report, we found that violative advertisements had often been disseminated for several months before letters were issued in 2004 and 2005. More than half of the violative DTC materials cited in the 2004 and 2005 letters were no longer being disseminated by the time the letter was issued. Delays in issuing regulatory letters limit FDA's effectiveness in overseeing DTC advertising and in reducing consumers' exposure to false or misleading advertising.

Finally, HHS commented that our discussion of research on DTC advertising implies that we statistically aggregated data from different studies to generate summary figures on the impact of DTC advertising on various types of consumer requests to their physicians. We have revised the report to clarify that the information we present is from the studies we reviewed and that we did not aggregate data across studies. HHS also provided technical comments which we incorporated as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of this letter. We will then send copies of this report to the Secretary of Health and Human Services, the Acting Commissioner of the Food and Drug Administration, and other interested parties. We will also make copies available to others who request them. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staffs have any questions about this report, please contact me at (202) 512-7119 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix III.

A handwritten signature in black ink, appearing to read "Marcia Crosse", with a long horizontal flourish extending to the right.

Marcia Crosse
Director, Health Care

Appendix I: Scope and Methodology

To examine trends in pharmaceutical industry spending on direct-to-consumer (DTC) advertising, promotion to medical professionals, and research and development of new drugs, we reviewed publicly reported data. For overall drug company spending from 1997 through 2005 on DTC advertising and promotion to medical professionals, we obtained data from IMS Health.¹ We interviewed knowledgeable IMS Health officials to verify the data's accuracy and the methodologies used for collecting them and reviewed related documentation and determined that the data were sufficiently reliable for the purposes of this report. In addition, we obtained data on drug company spending from 1997 through 2005 on research and development of new drugs from the Pharmaceutical Research and Manufacturers of America (PhRMA), which represents U.S. pharmaceutical research and biotechnology companies. For 2005, we reviewed more detailed data on DTC advertising by prescription drug from Nielsen Monitor-Plus, which were reported in the May 2006 edition of Med Ad News, a publication targeted to the pharmaceutical industry. For the PhRMA and Nielsen Monitor-Plus data, we reviewed related documentation and determined that the data were sufficiently reliable for the purposes of this report. The scope of our analysis focuses on trends since 1997 because in that year the Food and Drug Administration (FDA) issued its draft guidance clarifying the requirements for broadcast advertising.

To examine the relationship between DTC advertising and prescription drug spending and utilization, we conducted a literature review. We conducted a structured search of 33 databases that included peer-reviewed journal articles, dissertations, and industry articles issued from January 2000 through February 2006. We searched these databases for articles with key words in their title or abstract related to DTC advertising, such as various versions of the word “advertising,” “consumer,” “patient,” “physician,” “doctor,” and “return on investment.” We supplemented this list with searches of the references in articles identified through the database search. We also included articles cited during our interviews with representatives from advocacy organizations—Consumers Union and Public Citizen—and industry representatives from PhRMA, AstraZeneca Pharmaceuticals LP, and Pfizer Inc. From all of these sources, we

¹IMS Health data for spending on DTC advertising do not include spending to develop and maintain drug companies' Web sites or spending on sponsorship of sporting events. In addition, the data for spending on promotion to medical professionals do not include drug company spending on meetings and events, or spending on promotion that targets medical professionals other than physicians, such as nurse practitioners and physicians assistants.

identified over 600 articles published from 1982 through 2006. Within the more than 600 articles, we identified for detailed review 64 journal articles and dissertations that were original research and had subject matter directly relevant to the relationship between DTC advertising and prescription drug spending and utilization.

To examine the DTC advertising materials that FDA reviews, we reviewed applicable laws and regulations and data from FDA on the number and type of advertising materials that the agency receives and reviews. For materials submitted from 1997 through 2005, we obtained data from FDA's Advertising Management Information System database, which tracks the number of final advertising materials the drug companies submit to FDA at the time of their dissemination to the public. FDA officials told us that these data may contain errors because drug companies do not always properly identify the type of advertising material in their submission to FDA. For example, a DTC material may be incorrectly coded as a material directed to professionals. Although FDA officials do not know the extent to which such errors are entered into the database, based on our review of their data collection methods and our interviews with knowledgeable agency officials, we determined that these data were sufficiently reliable for reporting on trends in the volume of materials submitted to FDA. We also obtained data from FDA's Marketing, Advertising, and Communications Management Information System database—which tracks correspondence between the agency and drug companies—to determine the number of submissions of draft materials received by FDA from 1997 through 2005. We discussed these data with the responsible FDA official, and determined that they were sufficiently reliable for their use in this report. We also interviewed FDA officials, including staff who are directly responsible for reviewing DTC materials, about their processes for reviewing advertising materials. We did not examine the effectiveness of FDA's review of draft materials at preventing potentially violative materials from being disseminated.

To examine the number of FDA regulatory letters that cited DTC materials and FDA's process for issuing regulatory letters, we reviewed all letters issued by FDA from 1997 through 2005 citing prescription drug promotion and identified those that cited DTC advertising materials. We excluded regulatory letters that cited only materials intended to be given to consumers by medical professionals or that cited only materials directed to medical professionals. We then asked FDA officials to review our list and add letters we had not identified and remove letters that did not specifically cite DTC materials. As a result of this process, we identified 135 regulatory letters—citing materials promoting 89 different drugs—that

cited a violative DTC material. In our review of the regulatory letters, we did not evaluate the appropriateness of the cited violations or evaluate the legal sufficiency of the letters. We examined the content of FDA's most recent regulatory letters—the 19 regulatory letters, 6 warning letters and 13 untitled letters, FDA issued from 2004 through 2005—in order to determine the types of violations that FDA identified and the actions that the agency requested the drug companies to take. (See table 3.) Of these 19 regulatory letters, 18 cited violative materials for a single drug. In one instance, the letter cited materials promoting two drugs promoted by a single company.

Table 3: FDA Regulatory Letters Issued from 2004 through 2005 That Cited DTC Materials

Drug cited	Date of letter ^a	Condition	Drug company	Type of each cited advertisement
2004				
Warning letters				
MUSE	5/25/2004	Erectile dysfunction	VIVUS Inc.	Television Web site
Norvir	6/10/2004	Human immunodeficiency virus	Abbott Laboratories	Web site
Pamine	11/9/2004	Peptic ulcer	Bradley Pharmaceuticals Inc.	Web site
Untitled letters				
Crestor	12/21/2004	Cholesterol	AstraZeneca Pharmaceuticals LP	Print
Effexor	3/18/2004	Depression	Wyeth Pharmaceuticals	Radio
Kaletra	10/29/2004	Human immunodeficiency virus	Abbott Laboratories	Print Restroom poster
Paxil CR	6/9/2004	Social anxiety disorder	GlaxoSmithKline	Television
Seasonale	12/29/2004	Contraceptive	Barr Research Inc.	Television
Viagra	11/10/2004	Erectile dysfunction	Pfizer Inc.	Television 1 Television 2
Viramune	9/22/2004	Human immunodeficiency virus	Boehringer Ingelheim Pharmaceuticals Inc.	Print
Zyrtec-D 12hr	4/22/2004	Allergies	Pfizer Inc.	Web site
2005				
Warning letters				
Enbrel	2/18/2005	Plaque psoriasis	Amgen Inc	Television
Quadramet	7/18/2005	Pain associated with cancer	Cytogen Corporation	Radio Web site

Drug cited	Date of letter ^a	Condition	Drug company	Type of each cited advertisement
Zyrtec	4/13/2005	Allergies	Pfizer Inc.	Print 1
				Print 2
				Print 3
Untitled letters				
Celebrex and Bextra	1/10/2005	Osteoarthritis, rheumatoid arthritis, painful menstruation	Pfizer Inc.	Television 1
				Television 2
				Television 3
				Direct mail
Crestor	3/8/2005	Cholesterol	AstraZeneca Pharmaceuticals LP	Television
				Print 1
				Print 2
				Print 3
Levitra	4/13/2005	Erectile dysfunction	Bayer Pharmaceuticals Corporation	Television
Strattera	6/14/2005	Attention deficit hyperactivity disorder	Eli Lilly and Company	Television
Zoloft	5/6/2005	Major depressive disorder	Pfizer Inc.	Print

Source: GAO analysis of FDA regulatory letters.

^aRegulatory letters are available online from FDA, Center for Drug Evaluation and Research, *Warning Letters and Notice of Violation Letters to Pharmaceutical Companies*, <http://www.fda.gov/cder/warn/> (last accessed on Sept. 26, 2006).

We also reviewed FDA documentation to determine how long it took the agency to draft and issue the 135 regulatory letters it issued from January 1997 through December 2005. We used information from FDA records to obtain the date on which reviewers first began drafting a regulatory letter. These records also contained information about key meetings that occurred, internal consultations requested by FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC), and the comments obtained during the drafting and review of each regulatory letter. Because FDA does not track when the agency identifies a violation, we considered the date on which reviewers first began drafting a regulatory letter as the earliest date in the letter drafting and review process. For each of the 19 regulatory letters issued from 2004 through 2005, we obtained the date DDMAC formally submitted the draft letter to the Office of the Chief Counsel (OCC) from FDA's Agency Information Management System database. This system is designed to document the dates of key interactions between OCC and other FDA offices. OCC officials told us that the date DDMAC submitted draft regulatory letters to OCC was consistently documented in the system. Based on our

discussions with OCC officials and our review of similar dates recorded in DDMAC's case files, we determined that these data were sufficiently reliable for the purposes of this report.

To examine the effectiveness of FDA's regulatory letters, we focused on the 19 regulatory letters issued from 2004 through 2005 that cited DTC materials. We reviewed the files that FDA maintains for each advertised drug cited in these letters. These files contain correspondence from the drug companies, copies of advertising materials, and documentation of FDA actions. We reviewed FDA's correspondence with the drug companies to obtain information regarding the regulatory letters, the dates the violative advertisements started and ended, and the drug companies' compliance with any corrective action requested by FDA. The information we collected is based both on what drug companies reported in correspondence with FDA and, in some cases, what we obtained directly from the sponsoring drug company. We did not confirm the accuracy of the information drug companies reported to FDA or to us. We also identified the violations cited in the 135 regulatory letters FDA issued from 1997 through 2005.

We conducted our work from January 2006 through November 2006 in accordance with generally accepted government auditing standards.

Appendix II: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

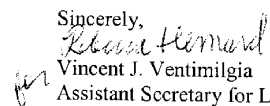
NOV 3 2006

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
Washington, DC 20548

Dear Ms. Crosse:

The Department of Health and Human Services has reviewed the U.S. Government Accountability Office's (GAO) draft report entitled, "[PRESCRIPTION DRUGS: Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising](#)" (GAO 07-54).

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

Vincent J. Ventimiglia
Assistant Secretary for Legislation

**GENERAL COMMENTS OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN
SERVICES (HHS) ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S
(GAO) DRAFT ENTITLED: PRESCRIPTION DRUGS: IMPROVEMENTS NEEDED IN
FDA'S OVERSIGHT OF DIRECT-TO-CONSUMER ADVERTISING" (GAO-07-54)**

The Department appreciates the opportunity to review and comment on this draft report. While the Department agrees with much of the description of FDA's oversight of direct-to-consumer (DTC) advertising by the Division of Drug Marketing, Advertising, and Communications (DDMAC), the Department disagrees with some of the report's conclusions and does not believe that GAO's particular recommendations address the problems identified in its conclusions.

General Comments

The draft report discusses topics that GAO identified as part of its Congressional request "to examine trends in DTC advertising and FDA's regulation and oversight of this advertising."

GAO recommends three actions to improve FDA's processes for identifying final and draft DTC advertising materials as a means of ensuring that it is identifying and reviewing the highest priority materials: (1) documenting criteria for prioritizing DTC materials that it receives for review, (2) systemically applying the documented criteria to all of the materials it receives, and (3) tracking which materials have been reviewed.

We do not believe these recommendations reflect a full understanding of the regulatory review process in DDMAC, specifically, how DDMAC chooses materials to review. The suggestion that DDMAC does not consider DTC materials that should have the highest priority is incorrect. First, DDMAC reviews all final and draft broadcast ads because these have the greatest potential impact. Second, it reviews other draft DTC pieces because this provides an opportunity to avoid problems, and it considers which of these to pursue according to the criteria listed on page 18 of the report. It is true that DDMAC does not review every one of the over 10,000 pieces in detail or in their entirety, but little would be gained from this and resources do not permit it.

FDA, like other regulatory agencies, exercises enforcement discretion in order to focus its limited resources on enforcement actions that would most impact public health. Although DDMAC does not document the criteria it uses to prioritize each DTC piece received for review, DDMAC has identified criteria that are systematically applied to identify workload priorities for review of both draft and final DTC materials that have the greatest impact on public health. The DDMAC management team, and in particular the DTC group leaders, work with all the DTC reviewers to ensure consistent application. DDMAC exercises judgment in continually reevaluating workload in light of these priorities, contingent on emerging scientific and regulatory events. The suggestion that each piece be reviewed under specified criteria, and that all reviews be documented, would require vastly increased staff to essentially review every piece in detail. What now happens is that experienced reviewers scan pieces for problems, recognizing our priorities, and choose the ones to pursue.

GENERAL COMMENTS OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT ENTITLED: PRESCRIPTION DRUGS: IMPROVEMENTS NEEDED IN FDA'S OVERSIGHT OF DIRECT-TO-CONSUMER ADVERTISING" (GAO-07-54)

The triage and review functions have been designed to operate in the continually expanding and complex realm of DTC-related submissions (both draft and final). Although, given our limited resources, we are unable to review every one of the thousands of DTC pieces that are submitted yearly, we believe the established processes best utilize these limited resources to effectively address DTC promotion and assure review of the most important materials.

We do not believe the recommendation that DDMAC track all of the materials it reviews would represent effective use of resources or address the problems GAO has identified. Given current resource levels, it would not be practical or cost-effective to spend time entering into a tracking system all of the materials that are considered, most of which are not reviewed fully. As noted, we devote resources to (1) providing advisory comments to industry on voluntarily submitted draft DTC materials (an activity to which reviewers devote the majority of their time in order to encourage voluntary compliance) and (2) reviewing all final DTC broadcast materials for possible enforcement actions, rather than to developing a system to document the fact that a piece was reviewed. Although, we do not dispute that, given sufficient resources, it would be helpful to have a state-of-the-art tracking system, we do not believe that adding administrative or tracking functions to reviewers' current duties would improve efforts to facilitate identification and review of high priority materials.

Finally, the report criticizes the agency for both the length of time it takes to issue warning and untitled letters and for the reduction in the total number of letters issued. The report attributes both concerns to the Department's 2001 directive requiring the FDA's Office of Chief Counsel (OCC) to review all warning and untitled letters. As the GAO is aware, the express purpose of the directive was to ensure that enforcement letters rest on a solid legal foundation, are credible, and will promote compliance. Given that, the Department is disappointed that the GAO has chosen not to examine the benefits of legal review, such as more defensible letters and better compliance after issuance, but instead has decided to focus only on the timeliness and quantity of letters issued. More pointedly, given the GAO's candid admission that it didn't look at the legal sufficiency of the letters cleared by OCC, the GAO simply isn't in a position to comment on whether legal review is good or bad.

Prior to the Department's directive, the letters the FDA sent were often not legally sustainable and, therefore, were regularly ignored by the regulated industry or, worse yet, not followed up by the agency. Recognizing that the agency's credibility would suffer if it was considered a paper tiger, the Department ultimately determined that a change was necessary and desirable. As part of that change, OCC was directed to make sure that every enforcement letter issued by the FDA rested on a solid legal foundation. To comply with the directive, OCC review assures that each enforcement letter (1) is logically coherent, internally consistent, and clear, (2) correctly alleges a violation of a legal requirement that is within FDA's authority to enforce, and (3) provides a sufficient bases for any subsequent enforcement action.

**GENERAL COMMENTS OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN
SERVICES (HHS) ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S
(GAO) DRAFT ENTITLED: PRESCRIPTION DRUGS: IMPROVEMENTS NEEDED IN
FDA'S OVERSIGHT OF DIRECT-TO-CONSUMER ADVERTISING" (GAO-07-54)**

When the FDA takes a position, companies must believe that the FDA can and will back it up by going to court if necessary. In the past, FDA warning and untitled letters did not always instill such a belief. Now, however, when a company receives an enforcement letter from the FDA it knows that the letter has been cleared by agency lawyers, and that the agency is prepared to go to court if necessary. As a result, companies take our letters more seriously and quickly react to the problems identified therein. Instead of sending multiple letters, one letter now suffices.

The FDA cannot review every piece of direct-to-consumer advertising. As a result, we must rely in great part on voluntary compliance. The OCC review has strengthened the quality and legal sustainability of the letters actually issued by the FDA and, by so doing, has paved the way for enforcement actions with real teeth. That, more than anything else, has encouraged voluntary compliance with our regulations.

General Research Comments

In general, we are concerned that the way in which the conclusions in the research section are described imply that GAO employed statistical aggregation on the results from all the reviewed research in order to make its conclusions. This is particularly evident in the statements on page 15 such as "...about one quarter of such consumers (ranging from 7 to 35 percent) requested a prescription..." (first paragraph, line 1). It is not evident from the summary whether GAO has chosen the average percentage, the median percentage, or employed some other method to arrive at this number.

Appendix III: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7119 or crosssem@gao.gov

Acknowledgments

In addition to the contact named above, Martin T. Gahart, Assistant Director; Chad Davenport; William Hadley; Cathy Hamann; Julian Klazkin; and Eden Savino made key contributions to this report.

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