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Report to the Ranking Member, Committee on Finance, U.S. Senate

July 2008

PRESCRIPTION DRUGS

FDA's Oversight of the Promotion of Drugs for Off-Label Uses

GAO-08-835

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Highlights

Highlights of GAO-08-835, a report to the Ranking Member, Committee on Finance, U.S. Senate

Why GAO Did This Study

The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), regulates the promotion of prescription drugs to ensure that promotional materials are not false and misleading and that they comply with applicable laws and regulations. Among other things, FDA prohibits drug companies from promoting drugs for off-label uses—that is, for a condition or patient population for which the drug has not been approved or in a manner that is inconsistent with information found on the approved drug label. Although doctors may prescribe drugs off label, it is not permissible for drug companies to promote drugs for off-label uses. FDA may take regulatory actions for violations, and may also pursue enforcement action through the Department of Justice (DOJ).

GAO was asked for information about the promotion of drugs for off-label uses. GAO reviewed (1) how FDA oversees the promotion of off-label uses of prescription drugs and (2) what actions have been taken to address off-label promotions. GAO examined documentation related to the promotion of drugs for off-label uses and FDA correspondence with drug companies on identified violations and obtained information from DOJ on relevant actions. GAO also interviewed officials at FDA and the HHS Office of Inspector General and representatives of national medical and pharmaceutical associations.

To view the full product, including the scope and methodology, click on GAO-08-835. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

FDA oversees drug promotion for off-label uses by reviewing promotional materials that drug companies submit to the agency. However, because FDA does not have separate oversight activities to specifically capture off-label promotion, its oversight occurs within a broader process that targets a variety of promotional violations. Furthermore, FDA reports it is unable to review all submissions because of the volume of materials it receives and prioritizes its reviews in order to examine those with the greatest potential impact on human health. However, FDA does not prioritize its reviews in a systematic manner but rather relies on its staff to sort through large volumes of material and select submissions for review. FDA is also hampered by the lack of a system that consistently tracks the receipt and review of submitted materials. To address these shortcomings, GAO recommended in 2006 that FDA track which materials it has reviewed. FDA has not acted on this recommendation and still lacks a standardized tracking system to monitor its review efforts. GAO believes that this recommendation remains valid. In addition to its reviews, FDA conducts monitoring and surveillance to identify violations that would not be identified through its review of submitted material—for instance, discussions between doctors and sales representatives. These efforts are also limited because FDA cannot observe all off-label promotion activities as they can take many forms and occur in a myriad of places.

FDA and DOJ have taken regulatory and enforcement actions against drug companies in response to off-label promotions. During calendar years 2003 through 2007, FDA issued 42 regulatory letters in response to off-label promotions requesting drug companies to stop dissemination of violative promotions. FDA took an average of 7 months to issue these letters from the time it first drafted them. In addition, drug companies that were cited for more serious violations took an average of 4 months to take the corrective actions requested. While FDA did not refer any of these violations to DOJ for enforcement action, during calendar years 2003 through 2007, DOJ settled both civil and criminal cases that involved, at least partially, off-label promotion. These actions were initiated as a result of violations identified by sources other than FDA and resulted in 11 settlements.

In commenting on a draft of this report, HHS raised concerns with GAO's assessment that FDA does not systematically prioritize all of the promotional materials it receives. It also stated that a tracking system would not improve the agency's ability to identify promotional violations. GAO found that FDA does not screen all promotional materials. GAO continues to believe that a tracking system would help ensure that staff screen all material received, facilitate a more systematic approach to FDA's reviews, and help the agency manage the program.

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Abbreviations

ACCME	Accreditation Council for Continuing Medical Education
AMA	American Medical Association
CME	Continuing Medical Education
DDMAC	Division of Drug Marketing, Advertising, and Communications
DOJ	Department of Justice
DTC	Direct-to-consumer
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FFDCA	Federal Food, Drug, and Cosmetics Act
HHS	Department of Health and Human Services
NDA	New Drug Application
OCC	Office of the Chief Counsel
OCI	Office of Criminal Investigation
OIG	Office of Inspector General
PhRMA	Pharmaceutical Research and Manufacturers of America

GAO
Accountability * Integrity * Reliability

United States Government Accountability Office
Washington, DC 20548

July 28, 2008

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

Dear Senator Grassley:

Drug companies provide medical professionals and consumers with information about prescription drugs in a variety of ways, such as direct-to-consumer (DTC) advertising on television or the Internet, presentations by drug company sales representatives, and patient brochures provided in physicians' offices. The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), regulates the promotion and advertising of prescription drugs.[1] Although drug companies are permitted to promote their drugs, these promotions may not be false or misleading and must comply with applicable laws and regulations.[2] Among other things, drug companies are prohibited from promoting drugs for off-label uses—that is, for a condition or patient population for which the drug has not been approved or in a manner that is inconsistent with information found in the drug's labeling that has been approved by FDA.

FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) has responsibility for overseeing materials and activities that promote prescription drugs and identifying potential violations. For example, in addition to off-label promotions, it may identify violations such as minimizing the risk of a drug or overstating a drug's safety or effectiveness. To do this, DDMAC reviews written materials submitted by drug companies, including final promotional materials that companies are required to submit at the time the materials are first disseminated to the public. DDMAC may also review submissions of draft promotional materials that drug companies voluntarily submit for advisory review. In addition to reviewing submitted materials, DDMAC conducts monitoring and surveillance of promotional activities that drug companies may engage

[1]We will refer to "promotion and advertising activities" as "promotion."

[2]See 21 U.S.C. § 352(a), (n), and 21 C.F.R. § 202.1(e) (2007).

in, such as sponsoring information booths and distributing literature at medical conferences. If a promotional violation is identified, the agency may take regulatory action by issuing one of two types of regulatory letters, depending on the severity of the violation. FDA may issue either an untitled letter or, for more serious violations, a warning letter. Both types of letters request the drug company to take specific actions, such as stopping the dissemination of violative materials and issuing corrections of previously distributed information. When drug companies fail to take appropriate action in response to regulatory letters, FDA may refer violations to the Department of Justice (DOJ) for enforcement actions. For example, FDA may work with DOJ to have a violative product seized. DOJ may opt to further investigate drug companies and prosecute them for violations identified by FDA, as well as for promotional violations identified by other sources.

While it is not permissible for drug companies to promote drugs for off-label uses, FDA does not regulate the practice of medicine and recognizes that physicians may determine that prescribing a drug off label constitutes good care.[3] Off-label prescribing occurs frequently. For example, a 2006 study found that more than 20 percent of prescriptions written for 100 of the 500 most commonly used prescription drugs, and 60 prescription drugs chosen by random selection, in the United States were for off-label use.[4]

However, concerns about the off-label use of drugs and associated promotions have mounted in recent years. Instances of patients being improperly medicated and consequently injured have been reported. In addition, the federal government, through DOJ, has reached settlements with drug companies for off-label promotion. For example, in May 2004,

[3]However, the federal government has placed limitations on reimbursements for drugs that have been prescribed off label in both the Medicare program—the federal health care program that serves the nation's elderly and disabled—and the Medicaid program—the federal-state health care program that serves low-income individuals. Although both programs make reimbursements for off-label prescriptions, the off-label use for a drug generally must be supported by its being listed in one or more of several named compendia. See, for example, 42 U.S.C. §§ 1395x(t)(2), 1395w-102(e)(1), 1396r-8(k)(6).

[4]D.C. Radley, S.N. Finkelstein, and R.S. Stafford, "Off-Label Prescribing Among Office-Based Physicians," *Archives of Internal Medicine*, vol. 166, no. 9 (2006). Similarly, we previously reported that one-third of the drug treatments prescribed by cancer physicians were for off-label uses and that more than half of cancer patients received at least one drug for an off-label indication. See GAO, *Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies*, GAO/PEMD-91-14 (Washington, D.C.: Sept. 27, 1991).

Pfizer, Inc. agreed to pay $430 million in connection with its promotion of the antiseizure drug Neurontin for a variety of off-label uses, such as bipolar disorder and migraines.[5]

You expressed concern about the potential impact of off-label promotion on physicians' prescribing practices and patients' safety and well-being, and interest in FDA's oversight of off-label promotion. This report examines (1) how FDA oversees the promotion of off-label uses of prescription drugs and (2) what actions have been taken to address off-label promotions.

To determine how FDA oversees the promotion of off-label uses of prescription drugs, we interviewed DDMAC officials about their review of promotional materials and their monitoring and surveillance efforts relating to off-label promotion. We also obtained data on the volume of final promotional materials submitted to FDA for review and FDA's responses to draft materials submitted by drug companies for advisory review. Based on interviews with DDMAC officials and our review of related documentation, we determined that these data were sufficiently reliable for the purposes of our report. We also interviewed DDMAC officials to obtain information about the process they use to prioritize their oversight efforts and the methods they use to identify potential promotional violations. We reviewed pertinent laws, regulations, and guidance applicable to each of these activities. We contacted representatives from the Pharmaceutical Research and Manufacturers of America (PhRMA), the American Medical Association (AMA), and the Accreditation Council for Continuing Medical Education (ACCME) to obtain their views on requirements related to off-label promotion. In addition, we reviewed various academic studies on off-label use and promotion.

To determine actions taken to address off-label promotion, we obtained all of the 117 regulatory letters FDA issued during calendar years 2003 through 2007 in response to violative promotions of prescription drugs. We reviewed the content of these letters to determine how often they cited off-label promotion versus other promotional violations. In addition, we

[5]Among other things, the settlement provides for a $21 million grant program designed to provide health care professionals and consumers information relating to prescription drugs, including drug marketing and the conditions for which drugs are prescribed. In June 2000, Pfizer, Inc. acquired Warner-Lambert, the drug company cited in the settlement, and agreed to comply with the terms of the settlement.

further analyzed the letters that cited off-label promotion to determine the specific circumstances of each violation, the market to which the promotion was directed, and whether the drug company had additional contact with FDA concerning violative promotional materials. We also reviewed all letters that FDA issued during calendar years 1997 through 2007 for violative promotions of drugs to determine if any of the off-label promotions we identified during calendar years 2003 through 2007 were repeat violations. We did not evaluate the appropriateness of cited violations or evaluate the legal sufficiency of these letters. We interviewed DDMAC officials on the process of issuing regulatory letters and also confirmed that our list of regulatory letters citing off-label promotion was complete and accurate. We reviewed available FDA documentation to determine the length of time taken to issue regulatory letters citing off-label promotion. To calculate this time period, we used the date on which FDA first drafted a regulatory letter as the earliest date in this process and the date the letter was issued as the last date in the process.[6] We discussed drug companies' responses to the regulatory letters and the monitoring of these responses with DDMAC officials. We supplemented this information by reviewing documentation associated with the regulatory letters to obtain additional details about drug companies' response and compliance with any corrective actions requested by FDA. Finally, because they may also become involved in investigations involving off-label promotion, we interviewed officials at FDA's Office of Chief Counsel (OCC) and Office of Criminal Investigations (OCI) and HHS's Office of Inspector General (HHS-OIG). We also obtained information from DOJ's Web site for calendar years 2003 through 2007 to identify settlements between drug companies and the federal government that involved off-label promotion. Our examination was limited to FDA's oversight of human drugs; we did not examine FDA's oversight of promotions for other types of products under FDA's jurisdiction.[7] We also did not include information on FDA's review of draft materials submitted to the agency under the accelerated approval process for new drugs to treat serious or life-threatening illnesses, or for the approval of new drugs when human efficacy studies are not ethical or feasible.[8] We conducted our work from September 2007

[6]We used the date that the agency first drafted a regulatory letter to calculate this time period because FDA does not track the date when violations are actually identified.

[7]For example, we did not review FDA's oversight of promotions of medical devices, such as diagnostic ultrasound products and X-ray machines, and biologics, such as vaccines. These products are beyond the scope of this review.

[8]21 C.F.R. pt. 314 subpts. H, I (2007).

through July 2008 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Results in Brief

FDA's review of the final and draft versions of promotional materials submitted to the agency by drug companies is its primary mechanism for overseeing the promotion of drugs for off-label uses. The agency does not have separate oversight activities designed specifically for off-label promotion. Instead, its oversight of off-label promotion occurs within a broad oversight process that targets all promotional violations. According to DDMAC officials, staff rely on a process to prioritize their review of submissions that is intended to address those submissions that have the greatest potential to impact public health. However, because DDMAC staff are not able to examine all submissions to the agency, this process is not systematically applied to all submissions. In addition, limitations in FDA's oversight process make it unlikely that the agency is able to detect all off-label violations that occur. FDA lacks a standardized tracking system to manage its reviews. In 2006, GAO recommended that FDA track which materials it has reviewed and the agency has not taken action to address this recommendation. However, FDA still does not track all submissions or the status of reviews, which further impedes its efforts to identify any potential promotional violations, including off-label promotion. As these are the issues that led us to our 2006 recommendation, we believe that this recommendation remains valid. DDMAC officials also told us that while they review most of the drafts submitted for advisory review, they can only review a small portion of final materials submitted for review. They attribute this to the high volume of materials submitted—over 68,000 final submissions were received in calendar year 2007 alone. In addition to its review of submitted materials, FDA has limited monitoring and surveillance efforts that are intended to detect violations that may be missed or would not be detected through FDA's review processes. However, the extent and variety of promotional activities that occur make it difficult for FDA to oversee them in a comprehensive manner. For example, FDA staff can only attend a small number of the thousands of continuing medical education (CME) activities that take place every year and depend on voluntary complaints from physicians to identify off-label promotions, such as statements made by sales representatives in physicians' offices when the information was not requested by the physician.

FDA and DOJ have taken regulatory and enforcement action against drug companies in response to off-label promotions. During calendar years 2003 through 2007, FDA issued 42 regulatory letters in response to off-label promotion, which was the third most common promotional violation identified by FDA during this time frame. Our analysis of FDA documentation showed that it took FDA an average of about 7 months to issue the 42 regulatory letters—19 untitled letters and 23 warning letters—from the time these letters were first drafted. Because violative materials remain in circulation prior to the issuance of regulatory letters, the length of time it takes FDA to issue these letters limits their effectiveness. In 2002, GAO recommended that the agency issue regulatory letters more quickly. As these are the issues that led us to our 2002 recommendation, we believe that this recommendation remains valid. According to DDMAC officials and our analysis, drug companies have generally complied with the agency's proposed actions as suggested in these letters. For example, in most instances, drug companies ceased dissemination of identified violative materials upon receipt of a regulatory letter. However, we found that it took drug companies an average of about 4 months to take corrective actions in response to 23 warning letters that were issued for the more serious violations. DDMAC officials told us that because drug companies have generally complied with FDA's requests in the untitled and warning letters, they have not taken any enforcement action through referrals to DOJ. However, we found that during the same time period, DOJ took action against drug companies in response to violative off-label promotions. DOJ enforcement action resulted in 11 settlements with drug companies that included allegations of off-label promotion. These settlements often involved promotional practices that are more difficult for FDA to detect, such as violative discussions between physicians and drug company sales representatives. While none of these actions were initiated by DDMAC, the agency's DDMAC, OCC, and OCI were ultimately involved in their resolution.

In commenting on a draft of this report, HHS raised concerns with our assessment that FDA's prioritization process is not systematically applied to all of the promotional materials it receives. However, we found that FDA does not screen all of the tens of thousands of final promotional materials it receives per year to determine which ones need to be reviewed. Without a systematic application of FDA's criteria to every submission, the agency cannot be certain that it is reviewing the highest-priority materials submitted or that violative materials are not being circulated. HHS also stated that a tracking system would not improve the agency's ability to identify promotional violations. We disagree. We continue to believe that a tracking system would help ensure that staff

systematically prioritize all materials and would provide key information for managing the program. HHS also provided technical comments, which we incorporated as appropriate.

Background

Before FDA will approve a new drug application (NDA), allowing the drug to be marketed in the United States, its manufacturer must demonstrate to FDA's satisfaction that the drug is safe and effective for its intended use and patient populations. The review process includes examination of the proposed drug labeling, which specifically cites, among other things, the conditions and population the drug has been approved to treat. After the NDA and labeling are approved, any promotional materials used or distributed by the drug companies must be consistent with and limited to the information included in the approved labeling. Drug companies that want to expand the approved uses for their products, and promote those new uses, must submit new safety and effectiveness data and obtain FDA's approval prior to marketing them for new uses.

The Federal Food, Drug, and Cosmetic Act (FFDCA) authorizes FDA to regulate the promotion of prescription drugs.[9] FFDCA and implementing regulations require that prescription drug promotional materials not be false or misleading.[10] FDA has issued implementing regulations that attempt to prevent overstatement in product claims and require balanced disclosure of side effects, contraindications, and warnings. They state, in part, that drug promotions may not recommend or suggest any use that is not in the approved labeling.[11] Any approved new drug promoted for an off-label use is "misbranded" and in violation of FFDCA.[12]

FDA has traditionally differentiated between industry-supported scientific and educational activities that are otherwise independent and nonpromotional from other industry activities that are neither. For drugs, only the latter have been treated as labeling or advertising and therefore subject to the applicable provisions of FFDCA and its implementing regulations. In 1997, Congress passed the Food and Drug Administration

[9]21 U.S.C. §§ 352(a), (n), 393(d)(2).

[10]21 U.S.C. § 352(a), (f)(1), (n); 21 C.F.R. § 202.1(e)(5)(i) (2007).

[11]21 C.F.R. § 202.1(e)(4) (2007); see also 21 C.F.R. §§ 201.100(c)(1) and 201.128 (2007).

[12]21 U.S.C. § 352(a), (f)(1), (n). See, e.g., *U.S. v. Articles of Drug*, 625 F.2d 665 (5th Cir. 1980).

Modernization Act (FDAMA), which included a provision authorizing drug manufacturers to disseminate journal articles and referenced publications on off-label uses under certain conditions.[13] The FDAMA provision expired on September 30, 2006. However, on February 15, 2008, FDA released draft guidance that recommends good practices for drug companies concerning the dissemination of articles and publications that address off-label use. Among other things, this draft guidance recommends that drug companies limit such activities to the distribution of reprints of peer-reviewed research from scientific or medical journals published by organizations with editorial boards that use experts who have demonstrated expertise in the subject of the article. The draft guidance also states that these reprints should not be material that is written, edited, or otherwise influenced by drug companies or individuals with financial ties to them, nor would false or misleading information be allowed.[14] While some aspects of the draft guidance are similar to the FDAMA provision and its implementing regulations, there are two key differences. The draft guidance does not address, recommend, or suggest that (1) reprints of journal articles and reference publications on off-label uses of drugs be previewed by FDA or (2) supplemental NDAs containing new safety and effectiveness data on the off-label use discussed in the reprint should be sent to FDA.[15]

FDA regulates the content of all drug promotional materials and activities, whether directed to medical professionals or consumers. These materials and activities may take many forms, as shown in table 1.

[13]Pub. L. No. 105-115, § 401, 111 Stat. 2296, 2356-65.

[14]The public comment period for this draft guidance closed on April 21, 2008. FDA is in the process of reviewing comments it received but has not yet established a date for finalizing the guidance.

[15]Previously, drug companies could submit the material to FDA for review 60 days prior to dissemination to take advantage of a "safe harbor provision," which resulted from litigation challenging the constitutionality of the FDAMA provision. The "safe harbor provision" was explained in a Federal Register notice, 65 Fed. Reg. 14286 (Mar. 16, 2000). DDMAC officials said that they received 79 such submissions. The provisions also required drug companies to submit new safety and effectiveness data on the off-label use to obtain FDA's approval for a new indication, but DDMAC officials could not provide information on how often that occurred.

Table 1: Examples of Drug Company Promotions

Type of promotion	Method of promotion
Printed materials	• Brochures • Magazine advertisements • Professional journal advertisements
Other media	• Television and radio advertisements • Web sites
Oral statements	• Discussions between physicians and drug company representatives in physicians' offices • Presentations by drug company representatives at conference booths • Speeches at drug-company-sponsored events

Source: GAO.

FDA does not generally regulate the exchange of scientific information, but when such information is provided by or on behalf of a drug company regarding one of the company's products, the information may be subject to the labeling and advertising provisions of the law and regulations. For example, while information provided at CME programs—such as medical conferences and professional gatherings intended to enhance physicians' knowledge and enable them to meet certain practice requirements—is not generally subject to FDA regulation, it will be if the program has been funded and substantially influenced by a drug company.[16] Similarly, FDA's position is that companies may respond to unsolicited requests for information from health care professionals, even if responding to requests requires the companies to provide information regarding off-label uses.

As of March 2008, DDMAC had the equivalent of 44 full-time staff devoted to overseeing prescription drug promotions. This oversight involves reviews of submitted materials and monitoring and surveillance efforts.

[16]However, CME programs are subject to review by the ACCME, which accredits CME providers by ensuring that they meet certain standards. For example, the ACCME helps to ensure that the programs themselves and any presenters do not violate FDA regulations by requiring disclosures of any conflicts of interest. According to the ACCME Annual Report, in 2006, 93,582 CME programs took place in the United States, reaching over 8 million physicians. www.accme.org/index.cfm/fa/home.popular/popular_id/127a1c6f-462d-476b-a33a-6b67e131ef1a.cfm (accessed on May 14, 2008.) Unlike CME programs whose content is independent of drug companies, FDA regulates educational programs that are substantively influenced by drug companies.

The two types of promotional materials submitted to the agency for review are:

- *Required submissions of final promotional materials*: Drug companies are required to submit all final materials associated with promotions to FDA when they are first disseminated to the public.[17] These materials include everything that a drug company may use as part of a promotion, such as print advertisements; professional slides, exhibit panels, and reprints; and Internet promotions. Once submitted to FDA, promotional materials are distributed to DDMAC staff. When a concern is identified, the agency determines whether it represents a violation and merits a regulatory letter.

- *Voluntary submissions of draft promotional materials*: Drug companies have the option of voluntarily submitting draft promotional materials to FDA for advisory review. For example, they may exercise this option before launching expensive promotions, such as a marketing campaign for a new drug or a new television advertisement.[18] For these draft materials, FDA may provide the drug company with advisory comments to consider before the materials are disseminated, particularly if claims are identified that could violate applicable laws and regulations. As part of its comments, FDA provides guidance to the drug company on how to address the agency's concerns regarding the promotional materials.[19]

FDA supplements its reviews of final and draft material that drug companies submit with monitoring and surveillance efforts. These efforts include attending medical conferences, reviewing drug company Web sites, and following up on complaints received.

[17]21 C.F.R. § 314.81(b)(3)(i) (2007).

[18]PhRMA issued guidance effective January 2006 that states that "[drug] companies should submit all new DTC television advertisements to FDA before releasing these advertisements for broadcast." PhRMA Guiding Principles: Direct to Consumer Advertisements about Prescription Medicines (Washington, D.C.: PhRMA, Nov. 2005), http://www.phrma.org/principles_and_guidelines/ (accessed on May 5, 2008).

[19]If FDA notifies the drug company that a draft material is not in violation and subsequently changes its opinion, the agency must notify the drug company in writing and provide it with a reasonable amount of time for correction before any regulatory action is taken. 21 C.F.R. § 202.1(j)(4) (2007).

Once DDMAC identifies a violation—whether it be detected through its review processes or its monitoring and surveillance activities—it makes a determination on whether to pursue regulatory action, by issuing an untitled letter or a warning letter.[20] The warning letter is issued for more serious violations with regulatory significance and may lead to enforcement action if corrections are not made. An untitled letter cites violations that do not meet this threshold. Both types of regulatory letters cite any identified violation and ask the drug company to cease dissemination of the violative promotion and any other promotions with the same or similar claims. A warning letter also goes a step further and requests that the company take action to correct the misleading impression left by the violative promotion. Such action may include issuing a correction in the same media as the original violative promotion or notifying appropriate health care professionals. DDMAC prepares these regulatory letters and, prior to their issuance, OCC reviews and approves them to ensure that the letters are legally sufficient and consistent with agency policy. FDA generally posts regulatory letters on its Web site within several days of issuance.[21] Upon receiving either type of letter, drug companies are requested to send FDA a written response within 10 business days. While FDA does not have explicit authority to require drug companies to act upon regulatory letters, when matters raised in these letters, particularly warning letters, are not resolved, the agency may initiate enforcement action through DOJ, which could include seizures of violative products and injunctions prohibiting the company from continuing off-label promotions. In addition, the Food and Drug Administration Amendments Act of 2007 authorizes FDA to impose civil monetary penalties against anyone disseminating false or misleading DTC advertisements, which could include promoting off-label use.[22]

OCC provides legal opinions within FDA and participates in both civil and criminal cases, including those related to off-label promotions. FDA's OCI conducts criminal investigations and may work closely with OCC as well as HHS-OIG and DOJ in conducting off-label investigations.

[20]DDMAC officials told us that FDA issues regulatory letters to request drug companies to take certain actions as a means of bringing about voluntary compliance with applicable laws and regulations. These letters do not require drug companies to take such actions.

[21]Food and Drug Administration, Center for Drug Evaluation and Research, *Warning Letters and Notice of Violation Letters to Pharmaceutical Companies* (Rockville, MD.: 2008), http://www.fda.gov/cder/warn/ (accessed on May 5, 2008).

[22]Pub. L. No. 110-85, § 901(d)(4), 121 Stat. 823, 940-42.

We previously reported on shortcomings in FDA's oversight of the promotion of prescription drugs in DTC advertising. In 2002 we reported that FDA's oversight was generally effective but had limitations in halting the dissemination of violative materials or in preventing companies from repeatedly committing violations.[23] We also reported that FDA took increased time to issue regulatory letters, therefore prolonging the time violative materials remained on the market. We recommended that HHS expedite its issuance of regulatory letters to ensure that misleading materials are withdrawn as soon as possible. In 2006, we reported that FDA reviews a small portion of the DTC materials it receives.[24] We also reported that it did not have a process to systematically prioritize its submissions for review. Consequently, we recommended that FDA develop such a process for all of the materials it receives and track which materials it has reviewed—a recommendation we believe remains valid. We also reported that FDA was taking longer to issue regulatory letters than it did in 2002 and we stated that the recommendation in our 2002 report—that the agency issue regulatory letters more quickly—remained valid.[25] In May 2008, we updated this work and testified that FDA still did not systematically prioritize its review of all of the DTC materials it receives and thus could not ensure that it was reviewing the highest-priority materials.[26] We also noted that the amount of time it takes to issue regulatory letters has continued to lengthen.

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

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

[25]In 2002, FDA implemented a policy change requiring all draft regulatory letters to be reviewed by OCC, to ensure that all warning and untitled letters were reviewed for "legal sufficiency and consistency with agency policy." We reported that this reduced the agency's ability to issue these letters in a timely manner in 2002 and reiterated this finding in 2006. GAO-03-177 and GAO-07-54.

[26]GAO, *Prescription Drugs: Trends in FDA's Oversight of Direct-to-Consumer Advertising*, GAO-08-758T (Washington, D.C.: May 8, 2008).

FDA's Oversight of Off-Label Promotion Consists Primarily of Review of Materials Submitted by Drug Companies, but It Is Unlikely to Detect All Violations

The primary mechanism FDA uses to oversee off-label promotions is its review of materials submitted by drug companies. The oversight of off-label promotions occurs within a broad review process meant to detect a wide range of promotional violations—the agency does not have separate activities designed specifically to detect off-label promotion of prescription drugs. DDMAC staff use a process to prioritize their review of submitted materials, but they do not apply this process systematically. In addition, limitations in FDA's oversight make it unlikely that it is able to detect all off-label violations that occur. For example, FDA lacks a tracking system to manage its review process. FDA also acknowledges that it cannot review all submissions because of the volume of materials it receives and that only a small portion of the required submissions of final promotional materials are examined for potential violations. Although the agency conducts additional monitoring and surveillance to detect violations that could not be identified through a review of submitted materials, the extent and variety of promotional activities make it difficult for FDA to monitor these in a comprehensive manner.

FDA's Oversight Process Emphasizes Reviews of Materials Submitted by Drug Companies and Is Supplemented by Monitoring and Surveillance

The primary mechanism FDA uses to oversee the promotion of drugs for off-label uses is to review promotional materials submitted to the agency by drug companies. DDMAC staff examine submitted materials for a variety of potential violations simultaneously, such as minimizing the risk of the drug or overstating the safety or effectiveness of the drug, as well as off-label promotions.

Although DDMAC staff are tasked with reviewing final versions of materials that are required to be submitted and draft materials voluntarily submitted for advisory review, officials emphasized that advisory review of draft materials is particularly important. They said that this is because the advisory review process encourages voluntary compliance and allows FDA to identify potential violations, including off-label promotion, before materials are disseminated to the public. FDA's goal is to review all draft materials submitted for advisory review. Consequently, DDMAC staff spend the majority of their time reviewing and responding to these voluntary submissions. DDMAC officials told us that responding to the requests for advisory review can be very time consuming and labor intensive because staff want to ensure that the agency identifies all potential violations during this time.

To manage the workload associated with their reviews of final materials that drug companies are required to submit and draft materials submitted for advisory review, DDMAC staff rely on a process to prioritize their

reviews that is intended to address those submissions that have the greatest potential to impact public health. DDMAC officials told us that DDMAC's priorities are regularly updated to reflect changes in agency needs and legal requirements. Currently, it prioritizes its reviews based on whether the promotion involves

1. an apparent, egregious violation;
2. a drug that has undergone recent labeling changes and updates to its risk information;
3. a television advertisement disseminated for the first time for a drug or indication, or certain draft promotions that are associated with drugs approved under FDA's accelerated approval process and that reflect central themes from a company's promotion;[27]
4. new promotional campaigns that reflect central themes from the company's promotion;
5. other television advertisements and other draft campaigns submitted under the accelerated approval process;
6. other new promotional campaigns; and
7. other issues of concern.

DDMAC officials acknowledged that this process for prioritizing its reviews is not systematically applied to all of the materials it receives. Absent a systemic approach, DDMAC staff sort through large volumes of materials submitted and use the process to review as many submissions as possible. During their reviews of both final and draft materials, staff may use their clinical knowledge about a particular type of drug and its history to help determine if a submission contains an off-label promotion. DDMAC staff are organized into therapeutic review groups by drug category, such as allergy medications, to maximize individual knowledge about specific drugs and the marketing issues related to those drugs. Staff are assigned

[27]Drug companies must submit to FDA draft promotional materials prior to dissemination for drugs approved under FDA's accelerated approval process. The accelerated approval process is authorized for drugs that treat serious or life-threatening illnesses. Under the accelerated approval process, drug companies are required to submit all promotional material, in draft form, during the preapproval process and, after a drug is approved, prior to dissemination. 21 C.F.R. § 314.550. See also, 21 C.F.R. § 314.640 (2006).

promotional materials based on their therapeutic review group. DDMAC officials told us that this organization allows staff to develop familiarity with certain types of drugs, making them knowledgeable about information in the approved labeling and better able to identify off-label promotions.

In addition to its reviews of submitted materials, FDA also engages in monitoring and surveillance efforts. These efforts are intended to detect violations that could not be identified through FDA's reviews—such as violative oral statements made by sales representatives in discussions with physicians. These efforts may also identify violations that may be missed by FDA's review of submitted materials. As part of their monitoring and surveillance efforts, DDMAC and other FDA staff may attend educational events, such as CME programs, to monitor for inappropriate promotions. For example, an FDA official attending a CME conference might obtain a brochure discussing off-label use, which should have been submitted to the agency but was never provided to the agency. AMA and ACCME officials acknowledged that even though there are safeguards built into the CME accreditation process to ensure presenter independence and CME compliance with FDA regulations, violations may still occur. FDA's monitoring and surveillance efforts also include reviewing and following up on complaints it receives. These may be submitted by a drug company's competitors, health care providers, consumers, and former drug company personnel who have knowledge about violative promotions. DDMAC officials said that these complaints may inform FDA of potentially inappropriate oral promotions and also provide a backup system for identifying violations that may be on submitted materials that FDA never examined.

Limitations in FDA's Oversight Process Make It Unlikely That All Off-Label Violations Are Detected

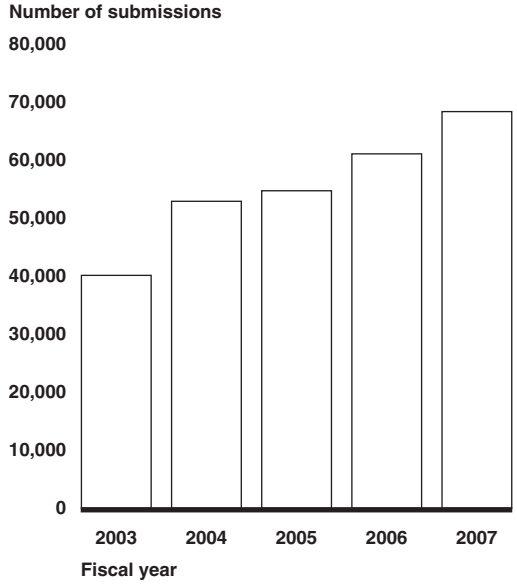
It is unlikely that FDA can detect all off-label promotion that occurs because of limitations in its oversight process for reviewing the promotion of prescription drugs. FDA's oversight is hampered by the lack of a system or process that consistently tracks its receipt and review of submitted materials. For example, DDMAC does not track the number of drafts it receives for advisory review. Despite its goal of reviewing all such submissions, DDMAC is unable to do so because, as officials explained, some drug companies release their promotions before they receive FDA's advisory comments. However, DDMAC does track the number of letters it

issues in response to the draft submissions staff are able to review.[28] Conversely, DDMAC tracks the number of final submissions it receives but does not track the number of the final submissions staff review. In 2006, GAO recommended that FDA track which materials it has reviewed but the agency has not taken action to address this recommendation. For example, DDMAC officials could not provide us with information on the prevalence of off-label promotions among material reviewed, the time it takes to complete reviews, or the status of their reviews. DDMAC officials said that obtaining this type of information is not currently possible due to the design of existing systems. As these are the issues that led us to our 2006 recommendation, we believe that this recommendation remains valid.

In addition, DDMAC officials told us that they receive substantially more materials than the agency can review. FDA received approximately 277,000 final promotional materials that drug companies were required to submit during calendar years 2003 through 2007. As shown in figure 1, FDA has received a steadily increasing number of final promotional materials during this time—the annual number increased from just over 40,000 in 2003 to over 68,000 in 2007. DDMAC officials generally attribute this growth to increases in DTC advertising as well as the increase in materials that drug companies are using to promote more complex new drugs.

[28]DDMAC issued approximately 3,000 letters in response to requests for advisory review during calendar years 2003 through 2007.

Figure 1: Number of Final Promotional Materials Submitted to FDA, Calendar Years 2003-2007



Source: FDA.

DDMAC and other FDA officials acknowledge that it is very difficult, if not impossible, for FDA's supplementary monitoring and surveillance efforts to identify all off-label promotion that may occur. This is because inappropriate promotion can take many forms and occur in a myriad of places. For instance, DDMAC and other FDA staff attend only a small number of the thousands of CME programs that occur each year. FDA is further challenged by the possibility that off-label promotional material, unrelated to a CME presentation, may be available to participants at nearby exhibition booths that drug companies often sponsor in conjunction with CME events. Although drug companies are required to submit such material to FDA for review, they might not do so or FDA might not review these materials until the conference or activity is

completed.[29] DDMAC officials told us that they consistently follow up on all complaints received as part of their monitoring and surveillance efforts, including those related to off-label promotion. According to DDMAC officials, FDA received and investigated an average of 150 complaints annually on possible promotional violations from 2003 through 2007. However, they could not provide us with data on the total number of their monitoring and surveillance efforts because this information is not tracked.

FDA's monitoring and surveillance efforts are further complicated by difficulties in assessing the merits of potential violations and the validity of complaints received. For example, according to FDA officials, the agency does not have sufficient authority to gather the key evidence necessary to determine whether educational activities are independent of the influence of drug companies. For example, DDMAC may not be able to determine whether a speaker at a CME event has been paid by the drug company to promote a drug for off-label uses. In such instances, DDMAC officials told us that they may work with other agencies, such as HHS-OIG and DOJ, which have the necessary investigative tools, such as subpoena authority, to investigate. Similarly, complaints can be difficult to validate. For example, a physician may complain to FDA about promotional material that was shown during a sales visit, but FDA staff may not be provided or have access to the material and therefore may be unable to determine if its use was violative. In addition, because FDA allows the exchange of information upon a request from a physician, it may be difficult to determine if information a sales representative provided orally to a physician was not requested. Without physicians' complaints, however, FDA would be unaware of these violative conversations. FDA not only depends on a physician's initiative to make a complaint but also on the physician's knowledge of when such conversation is inappropriate.[30]

[29]While FDA supports the full exchange of scientific information, including dissemination of scientific findings in scientific or lay media, it regulates promotional activities involving off-label drug use and takes action where such activities are inconsistent with the applicable laws and regulations. For example, when activities are performed by or on behalf of the drug companies that market the products being discussed (e.g., company-sponsored dinner meetings), these activities would be regulated by FDA as promotion and the materials used for the programs would have to be submitted to FDA. See 21 C.F.R. § 314.81(b)(3)(i)(2007).

[30]AMA is currently developing programs to educate physicians about inappropriate drug company promotional behavior, including off-label promotion, with funds received through the Neurontin settlement. AMA was one of 28 grantees receiving such funds.

Regulatory and Enforcement Actions Have Been Taken in Response to Off-Label Promotions

FDA and DOJ have taken regulatory and enforcement actions against drug companies for violative off-label promotions. During calendar years 2003 through 2007, FDA issued 42 regulatory letters—23 warning letters and 19 untitled letters—in response to off-label promotions. However, it took FDA an average of about 7 months to issue these letters, during which time violative material remained in the market. Most of the off-label promotional violations cited in those regulatory letters were identified through FDA's review of required drug company submissions. The promotional violations typically were targeted toward physicians and other medical professionals. According to DDMAC officials and our own analysis of correspondence between drug companies and FDA, drug companies have generally complied with the agency's directives as suggested in these letters, but may not have always done so in a timely manner. For example, it took drug companies receiving warning letters issued in response to the more serious violations an average of 4 months to take corrective action. According to DDMAC officials, they did not refer any violations to DOJ for enforcement action during 2003 through 2007. However, DOJ initiated civil and criminal enforcement actions in response to instances involving off-label promotion it identified from other sources. DOJ actions resulted in 11 settlements with drug companies that dealt, at least partially, with off-label promotion. While none of these were initiated by DDMAC, entities within FDA were ultimately involved in their resolution.

FDA Issued 42 Regulatory Letters Citing Off-Label Promotion in the Past 5 Years

Overall, FDA issued 117 regulatory letters for promotional violations during calendar years 2003 through 2007. However, according to DDMAC officials, there were more identified violations than those for which FDA issued regulatory letters because FDA prioritizes violations. Specifically, they said that in this regard, FDA's first priority is to issue warning letters because they generally address the most serious violations. For less serious violations—those involving untitled letters—these officials said that the issuance of such letters may be delayed, depending on the agency's workload. Our analysis of the 117 regulatory letters indicates that off-label promotion was the third most common violation, cited in 42, or approximately 36 percent, of the regulatory letters, as shown in table 2.

Table 2: Frequency of Violations in 117 Regulatory Letters, Calendar Years 2003-2007

Cited violation	Number of regulatory letters	Percentage of total letters[a]
Omission or minimization of risk	95	81
Overstated effectiveness or unsubstantiated effectiveness claims	54	46
Off-label promotion	42	36
Unsubstantiated superiority or comparative claims	40	34
Failure to submit required material to FDA	18	15
Other	27	23

Source: GAO analysis of FDA regulatory letters.

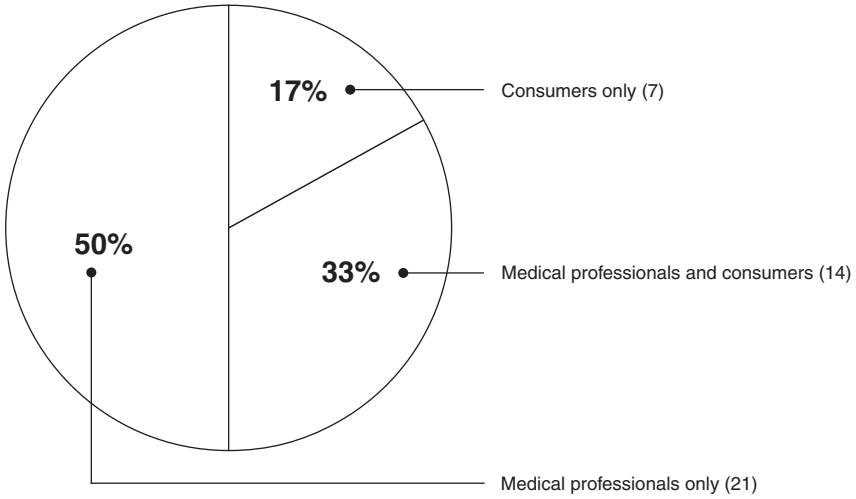
[a]Percentages do not add to 100 because most letters cite more than one violation.

Our analysis of the 42 regulatory letters citing off-label promotion indicates that review of submissions was the primary manner in which FDA identified off-label promotion. Specifically, for 31 of these letters, or 74 percent, FDA identified at least one violative promotion through its review of required submissions of final promotional materials.[31] Fourteen letters indicate that FDA identified at least one violative promotion through monitoring and surveillance activities. For more information on the off-label promotions cited in the 42 letters, see appendix I.

Half of the promotions cited in the 42 regulatory letters were targeted toward physicians and other medical professionals. Our analysis showed that 21 of the 42 off-label regulatory letters were issued in response to off-label promotions that included materials such as professional journal ads and exhibit panels, which solely targeted physicians and other medical professionals. Seven letters were issued in response to promotions directed solely to consumers, such as DTC magazine, television, or radio advertisements. The remaining 14 letters addressed promotions directed toward both medical professionals and consumers, such as product Web sites, as shown in figure 2.

[31]Regulatory letters may cite more than one promotion. In addition, FDA may cite violations it identified through submissions and through monitoring and surveillance in the same letter. For example, one letter cited an exhibition panel, which was submitted to FDA for review, and promotional material on the drug company's Web site that FDA identified through monitoring and surveillance.

Figure 2: Targeted Audience for Off-Label Promotions



Source: GAO analysis of FDA regulatory letters.

Our analysis of FDA documents related to the 42 regulatory letters citing off-label promotion indicated that it took FDA an average of about 7 months to issue the letters after DDMAC staff first drafted the letters.[32] For example, on March 7, 2006, FDA drafted a warning letter to Alcon, Inc. for off-label promotion, among other things. Over 7 months later, on October 20, 2006, FDA issued the letter. In 2002, GAO recommended that the agency issue regulatory letters more quickly. Because violative materials remain in circulation prior to the issuance of related regulatory letters, the length of time it takes FDA to issue these letters limits their effectiveness. As these are the issues that led us to our 2002 recommendation, we believe that this recommendation remains valid.

According to DDMAC officials, drug companies sent FDA written responses to the regulatory letters, and in most instances, they ceased dissemination of identified violative materials upon receipt of a regulatory

[32]FDA could not provide us with data on when the final material was first disseminated or when FDA identified a potential violation. Therefore, we used the date FDA first drafted the regulatory letter and the date of issuance of the letter to determine how long it takes the agency to issue a regulatory letter. We calculated the average length of time using data from 40 of the 42 identified off-label regulatory letters. We were unable to determine from FDA's documentation the date the regulatory letter was drafted for the remaining 2 letters.

letter.[33] However, DDMAC officials noted that there were occasions when they engaged in extensive discussions with drug companies that challenged the agency's assessment of a violation or the action requested in the regulatory letter. For example, a drug company may seek to negotiate with FDA in order to avoid having to take corrective actions, such as retracting an expensive DTC advertisement. DDMAC officials told us that during calendar years 2003 through 2007, FDA did not have to reverse any of its regulatory letter decisions as a result of such negotiations. Although FDA cannot ensure that a drug company has ceased dissemination of all violative materials related to a regulatory letter, it obtains a company's written agreement to stop dissemination of such materials, ensures that the list of materials a company is to stop disseminating is comprehensive, and reviews any new material submitted by the company for 6 months after issuance of a regulatory letter.

Twenty-three of the 42 off-label regulatory letters issued were warning letters, which, according to DDMAC officials, are issued for more serious violations than those cited in untitled letters. Ultimately, they said all but one company—which was issued a warning letter on May 25, 2007, and remained in negotiations with FDA as of April 22, 2008—had taken the necessary action requested in these warning letters. Consequently, DDMAC did not refer any violations regarding off-label promotions to DOJ for enforcement action. However, corrective action may not have always occurred in a timely manner. Our review of FDA documentation related to the 23 warning letters showed that it took drug companies an average of 4 months to implement corrective action from the time FDA issued the regulatory letter.[34] For example, on September 14, 2006, FDA issued a warning letter to Reliant Pharmaceuticals, Inc. for, among other things, off-label promotion of its drug Rythmol SR. Following the company's formal response letter on September 29, 2006, FDA and Reliant Pharmaceuticals, Inc. participated in at least three teleconferences and FDA wrote two letters in response to Reliant's proposed corrective action. Over 7 months after the letter was issued, the drug company disseminated the first set of corrective materials on April 17, 2007.

[33]Regulatory letters also request that drug companies remove all other promotional materials that make similar claims as the identified violative promotional materials. FDA continues to monitor related promotions by reviewing all submissions related to that drug for 6 months.

[34]Our analysis is based on 22 of the 23 warning letters citing off-label promotion, which have been resolved.

While DDMAC officials told us that drug companies have generally complied with FDA requests in the 42 regulatory letters, such letters do not prevent drug companies from repeatedly disseminating violative promotional materials. Our analysis of the 42 regulatory letters showed that for 11 of the 42 drugs cited in those letters for off-label promotion, FDA had issued regulatory letters citing off-label promotion in the past, as shown in table 3. For example, on March 18, 2004, Wyeth Pharmaceuticals was issued an untitled letter citing off-label promotion, among other things, for its drug Effexor XR. Prior to that letter, FDA had issued two other regulatory letters issued for off-label promotion of Effexor XR and Effexor, a related drug, on October 11, 2000, and June 25, 1997, respectively. Additionally, in another 2 of the 42 drugs FDA had prior communication with the drug companies about off-label promotion concerns.

Table 3: Drugs for Which FDA Cited Off-Label Promotion in More Than One Regulatory Letter

		Off-label promotion cited in FDA letter	
Drug product (company)[a]	**Approved condition**	**Most recent letter (CY 2003- 2007)**	**Prior letters**
Ciloxan (Alcon Research, Ltd.)	Specific eye infections	Letter cited oral statements by company representatives—specifically, statements by the representatives claiming that Ciloxan is safe and effective to treat otitis media and otitis externa. (7/18/2003)	• Letter cited a sales aid, a brochure, and "homemade" promotional materials that claim that Ciloxan treats pink eye in 3 days. However, the letter stated that the dosing regimen for pink eye is 7 days. (6/12/2000) • Letter cited a sales aid that claims that Ciloxan may be used as a prophylaxis in eye surgery. However the letter stated that Ciloxan is only indicated for infections caused by specific organisms. (4/15/1999)
Climara (BERLEX Laboratories, Inc.)	Certain menopausal symptoms	Letter cited a professional journal ad and exhibit panel that suggest that Climara has been demonstrated to be useful in treating hypertension, hypertriglyceridemia, or gallstones. (1/6/2003)	• Letter cited convention panels that claim Climara is as effective as Premarin. The letter stated Climara had not been shown to be as effective as Premarin in treating osteoporosis. (10/21/1998) • Letter cited a 1997 desk calendar that claims there are cardiovascular benefits from prolonged use of Climara. The letter stated that this claim has not been proven. (7/22/1997) • Letter cited mailing targeting customers with prescriptions for a competing treatment (Estraderm) and the mailing failed to disclose that Climara is not approved for all uses for which Estraderm is approved. (3/26/1997)
Diovan (Novartis Pharmaceuticals Corporation)	High blood pressure and heart failure (in specific instances)	Letter cited a sales aid that claims Diovan is effective in treating patients with type 2 diabetes and high blood pressure to preserve renal function. (4/21/2004)	• Letter cited a sales presentation that implied Diovan is useful for decreasing cardiovascular morbidity and mortality and treating patients with congestive heart failure. (9/23/1999)
Effexor XR (Wyeth Pharmaceuticals)	Major depressive disorder	Letter cited a radio advertisement and states that the ad does not draw a clear distinction between major depressive disorder and normal periodic feelings of low interest or energy. (3/18/2004)	• Letter cited various promotional materials that depict children and stated that the disclaimer indicating that the efficacy and safety of Effexor XR for pediatric use has not been established is not prominent. (10/11/2000) • Letter cited journal ads and stated that the ads imply that Effexor[b] has been shown to be safe and effective in depressed patients with concomitant cardiovascular disease, and Effexor has not been evaluated for this condition. (6/25/1997)

Drug product (company)[a]	Approved condition	Off-label promotion cited in FDA letter	
		Most recent letter (CY 2003- 2007)	Prior letters
Flonase (GlaxoSmithKline)	Nasal symptoms related to types of allergic and nonallergic rhinitis in adults and children 4 years of age or older	Letter cited a professional detail aid that fails to reveal that the safety and effectiveness of Flonase have not been established for children below 4 years of age. (5/7/2007)	• Letter cited a radio and newspaper print ad that claims Flonase is equivalent to oral antihistamines. It stated that Flonase has not been approved to treat nonnasal symptoms while oral antihistamines are approved to treat those symptoms. (6/19/2003) • Letter cited television ads that claim Flonase relieves postnasal drip. The letter stated that there is not substantial evidence demonstrating that Flonase is effective in treating this symptom. (3/10/2000)
OxyContin (The Purdue Frederick Company)	Pain relief under specific circumstances	Letter cited professional journal ads that promote OxyContin for use in a much broader range of patients with pain than has been proven safe and effective. (1/17/2003)	• Letter cited a professional journal ad that claims, among other things, that any dose of OxyContin can be used for the treatment of moderate to severe osteoarthritis pain. Such claims, according to the letter, are not supported. (5/11/2000)
Paxil CR (GlaxoSmithKline)	Social anxiety disorder	Letter cited a television ad that suggests that anyone experiencing anxiety, fear, or self-consciousness in social or work situations is an appropriate candidate for Paxil CR. (6/9/2004)	• Letter cited a T-shirt distributed at a health fair. The letter stated that the ad implies that Paxil[b] is a product that is useful in children; however, the safety and effectiveness of Paxil in children have not been established. (3/9/1998)
Pravachol (Bristol-Myers Squibb Company)	Prevention of cardiovascular events in patients with diagnosed coronary heart disease and prevention of coronary events in patients who have high cholesterol but are not diagnosed with coronary heart disease	Letter cited ads and other promotions that imply Pravachol is approved for prevention of stroke in patients who do not have clinically evident coronary heart disease. (8/7/2003)	• Letter cited a professional visual aid that fails to convey that Pravachol should be used in addition to diet and other measures and is not indicated to reduce heart attacks and lower cholesterol when used alone. (3/29/2001) • Letter cited two journal ads that feature women and imply that Pravachol reduces the risk of a first heart attack in women up to one-third. However, the letter stated that it has not been proven if Pravachol will reduce the risk of a first heart attack for women. (10/19/1998) • Letter cited a newspaper and broadcast ad that do not adequately convey that Pravachol should be used in addition to diet and other nonpharmacological measures. (5/1/1998) • Letter cited brochures and a journal ad that fail to prominently present that Pravachol is indicated as an adjunct to diet. (1/26/1998)

Drug product (company)[a]	Approved condition	Off-label promotion cited in FDA letter: Most recent letter (CY 2003- 2007)	Off-label promotion cited in FDA letter: Prior letters
Provigil (Cephalon, Inc.)	Improve wakefulness in specific groups of patients with excessive sleepiness	Letter cited a promotional piece that stated that Provigil is safe and effective for use in the treatment of various disorders associated with fatigue, sleepiness, or inattentiveness. The letter stated that Provigil is not indicated for fatigue and is only indicated for specific patients with excessive sleepiness. (2/27/2007)	• Letter cited promotional materials that implied that Provigil is safe and effective for use in the treatment of sleepiness, tiredness, decreased activity, lack of energy, and fatigue. The letter stated that Provigil is not indicated for such symptoms. (1/3/2002)
Tracleer (Actelion Pharmaceuticals US, Inc.)	Pulmonary arterial hypertension in patients with specific symptoms	Letter cited the product Web site that fails to present the fact that Tracleer is only indicated for patients with specific symptoms. (7/20/2005)	• Letter cited statements made by a company representative suggesting that Tracleer may be useful in treating patients with congestive heart failure. Such treatment, according to the letter, is not supported by the clinical evidence. (10/30/2002)
Viread (Gilead Sciences, Inc.)	Combination antiretroviral treatment for HIV-1 infection	Letter cited oral statements made by a company representative that failed to mention that Viread is only approved for use in combination with other antiretroviral agents. (7/29/2003)	• Letter cited oral statements by a company representative who stated that Viread was approved for a broad indication and that it was a miracle drug. (3/14/2002)

Source: GAO analysis of FDA regulatory letters.

Note: To determine past FDA enforcement action related to the 42 regulatory letters citing off-label promotion that FDA issued during calendar years 2003 through 2007, we reviewed FDA's Web site for any related regulatory letters the agency may have issued as early as 1997.

[a]Company name reflects information in the most recent regulatory letter.

[b]This drug is a variation of the drug cited in the most recent regulatory letter. It is a timed release version of that drug, used to treat the same condition(s) and promoted by the drug company under the same name.

Eleven Settlements Related to Off-Label Promotion Have Occurred in the Past 5 Years

According to DDMAC officials, they did not refer any violations to DOJ for enforcement action during calendar years 2003 through 2007 because drug companies have generally complied with requests made in FDA's regulatory letters during that time period. However, in the same time period, DOJ pursued a number of alleged violations in response to off-label promotion that it identified from other sources. Specifically, DOJ enforcement action resulted in 11 settlements with drug companies, which involved, at least partially, allegations of off-label promotion and resulted in, among other things, a monetary settlement. These settlements involved the types of promotional practices that are most difficult for FDA to identify, such as violative discussions between physicians and drug

company sales representatives. For example, at least 3 of the settlements involved specific allegations of off-label promotion between sales representatives and physicians. For more information on the alleged actions by drug companies, see appendix II.

The resulting monetary settlements ranged from almost $10 million to over $700 million.[35] For example, in September 2007, Bristol-Myers Squibb Company agreed to pay over $500 million for, among other things, promoting its drug Abilify—approved to treat schizophrenia and bipolar disorder—for pediatric use and for the treatment of dementia-related psychosis. In this instance, DOJ alleged that Bristol-Myers Squibb Company created a group of salespeople to target nursing homes where dementia is much more prevalent than schizophrenia or bipolar disorder. See table 4 for a summary of the 11 settlements negotiated by DOJ.

[35]Some settlements include money for offenses not related to the alleged off-label promotion.

Table 4: Settlements Involving Off-Label Promotion, Calendar Years 2003-2007

Date	Drug company	Drug name	Approved indication	Alleged off-label promotion	Settlement amount[a] (nearest $100,000)
May 2004	Pfizer, Inc.	Neurontin	Adjunctive or supplemental antiseizure use by epilepsy patients	Bipolar disorder, various pain disorders, Amyotrophic Lateral Sclerosis, attention deficit disorder, migraines, etc.	$430,000,000
Dec. 2005	Eli Lilly and Company	Evista	Prevention and treatment of osteoporosis in postmenopausal women	Prevention and reduction in the risk of breast cancer and reduction in the risk of cardiovascular disease	$36,000,000
Oct. 2005	Serono, S.A.	Serostim	AIDS wasting—the involuntary loss of more than 10 percent of body weight, plus more than 30 days of either diarrhea or weakness and fever	Lipodystrophy and body cell mass wasting	$704,000,000
Aug. 2006	Schering-Plough Corporation	Temodar and Intron A	Certain types of brain tumors, specific types of cancer, and chronic hepatitis B and C	Other types of brain tumors and metastases and superficial bladder cancer	$435,000,000
Oct. 2006	InterMune, Inc.	Actimmune	Disorders of the immune system caused by defects in immune system cells and severe malignant osteopetrosis	Lung scarring	$36,900,000
Apr. 2007	Pfizer, Inc.	Genotropin	Certain growth failure and related diseases in children and adults	Anti-aging, cosmetic use, and athletic performance enhancement	$34,700,000
Apr. 2007	Cell Therapeutics, Inc.	Trisenox	A specific and rare type of leukemia	Various forms of cancer	$10,500,000
May 2007	Medicis Pharmaceutical Corporation	Loprox	Fungicide for patients over 10 years of age	Treatment for children under the age of 10	$9,800,000
May 2007	The Purdue Frederick Company	OxyContin	Management of moderate to severe pain in specific instances	Wider pool of patients and conditions	$635,500,000
July 2007	Jazz Pharmaceuticals, Inc.	Xyrem	Weak or paralyzed muscles and excessive daytime sleepiness in narcolepsy patients	Fatigue, insomnia, chronic pain, weight loss, depression, bipolar disorders, etc.	$20,000,000
Sept. 2007	Bristol-Myers Squibb Company	Abilify	Treatment of adult schizophrenia and bipolar disorder	Pediatric use and dementia-related psychosis	$515,000,000

Source: Compiled from DOJ's Web site (www.usdoj.gov), HHS Web sites (www.cancer.gov and www.fda.gov), and FDA's OCC.

Note: For the purposes of this report, we have defined an off-label settlement to be any civil and/or criminal settlement or disposition of a matter where a sponsor's promotion of a drug for a use not contained in FDA-approved labeling was investigated, regardless of whether that alleged conduct was the basis for the ultimate disposition.

[a]Settlement amounts may include penalties for offenses not involving off-label promotion.

FDA had previously taken action against the drug companies with which DOJ reached settlements. We reviewed regulatory letters that FDA issued to drug companies from calendar years 1997 through 2007 for the same 12 drugs cited in the 11 settlements. This review indicated that, since 1997, FDA had identified promotional violations and issued one or more regulatory letters to drug companies for 7 of the 12 drugs. Of these 7 drugs, drug companies received regulatory letters for 5 drugs that cited off-label promotion. For 1 of these 5 drugs, the drug company received an FDA regulatory letter in June 2001 citing off-label promotion that was directly linked to the settlement. In response to the letter, the drug company assured FDA that the cited violation was an isolated incident. In the 2006 settlement, the company agreed, among other things, to plead guilty to criminal conspiracy to make false statements to FDA regarding its promotion cited in the 2001 regulatory letter. Specifically, the company acknowledged in the settlement that it knowingly misled FDA by claiming the violation was an isolated incident instead of a nationwide campaign. The regulatory letters FDA issued to drug companies for the other 4 drugs cited companies for off-label promotions that were not cited as the basis for the settlement. For example, for 1 of these 4 drugs, FDA issued an untitled letter to the drug company in September 2000, citing off-label promotion in a submitted DTC television advertisement. The related December 2005 DOJ settlement, however, was in response to off-label promotion conducted by the drug company's sales representatives and not the DTC advertisement cited in FDA letter. Table 5 provides information on the 12 drugs cited in the 11 settlements for off-label promotion and any prior regulatory letters issued by FDA.

Table 5: FDA Regulatory Letters Issued during Calendar Years 1997 through 2007 for Drugs Cited in Settlements, Involving Promotional Violations, Calendar Years 2003-2007

Drug name cited in off-label settlement (2003-2007)	FDA letters citing promotional violations (1997-2007)	Letters citing off-label promotion	Letters citing off-label promotion related to settlement
Neurontin	June 2001		
	July 2002		
Evista	November 1997		
	December 1998	✓	
	January 1999		
	September 2000	✓	
Serostim	April 1999		
Temodar	June 2001	✓	✓
Intron A	None		
Actimmune	None		
Genotropin	December 2001	✓	
Trisenox	None		
Loprox	March 2000	✓	
OxyContin	May 2000		
	January 2003	✓	
Xyrem	None		
Abilify	None		

Source: GAO analysis of FDA regulatory letters issued during calendar years 1997 through 2007 and DOJ information on settlements involving off-label promotion.

While DDMAC did not refer the violations to DOJ that resulted in the 11 settlements, it participated in their resolution. Specifically, DDMAC officials told us that they provided input to DOJ, such as information on whether the matter promoted off-label use or was otherwise violative, as well as opinions on the seriousness of the violation. Similarly, FDA's OCC and OCI participated in almost all of the investigations by providing legal counsel and conducting criminal investigations, respectively. Specifically, in all 11 settlements, one or more of FDA's offices—OCC, OCI, or both—were involved. In many of those instances, FDA became involved at DOJ's request and remained involved from the preliminary investigation through the final settlement. FDA's OCC and OCI officials told us that these investigations can be long term and very resource intensive. According to an FDA official, FDA is currently working on approximately 40 investigations regarding off-label promotion.

Agency Comments and Our Evaluation

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

HHS's comments focused on our discussion of FDA's process for prioritizing and tracking promotional materials submitted by drug companies for review. First, HHS raised concerns with our finding that DDMAC staff do not systematically prioritize all of the materials they receive. HHS stated that DDMAC staff apply prioritization criteria systematically to, among other things, the advisory submissions they receive. In addition, HHS stated that DDMAC staff also use criteria to determine which of the submissions of disseminated materials—that is, those final materials submitted for review—should be examined. However, we found no evidence that FDA systematically prioritizes all of the submissions it receives. We found that DDMAC staff do not screen all of the tens of thousands of final promotional materials they receive per year to determine which ones need to be reviewed. This means that FDA is not systematically applying its prioritization criteria to the majority of submissions the agency receives. We recognize that the volume of materials FDA receives presents a challenge for completing a detailed review of each submission, but without a systematic application of its criteria to screen submissions, it cannot be certain that it is reviewing the highest-priority materials or that violative materials are not being circulated. Applying the current criteria to the submissions DDMAC staff review, even if done consistently, is not the same as systematically screening all submissions in order to determine which ones should be reviewed.

Second, HHS commented that a tracking system would not improve the agency's ability to identify promotional violations nor would it change which submissions are actually reviewed. HHS said that such a system would not enable DDMAC to more efficiently regulate off-label promotion. We disagree. We continue to believe that, as we recommended in 2006,[36] a tracking system would facilitate a more systematic approach to DDMAC's reviews, would allow FDA to more readily group materials for review, and could enhance its monitoring and surveillance efforts by providing data on materials reviewed and the findings of those reviews. In short, a simple tracking system would provide key information for managing the program.

[36] GAO-07-54.

HHS did not comment on our reiteration of our 2002 recommendation that the agency issue regulatory letters more quickly.[37] HHS also provided technical comments, which we have incorporated as appropriate.

As agreed with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days after its issuance date. At that time, we will send copies to the Secretary of HHS, the Commissioner of FDA, and other interested parties. In addition, the report will be available at no charge on GAO's Web site at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.

Sincerely yours,

Marcia Crosse
Director, Health Care

[37] GAO-03-177.

Appendix I: FDA Regulatory Letters That Cited Off-Label Promotion, Calendar Years 2003-2007

Drug cited	Date of letter	Drug company	Approved condition	Off-label promotion cited
Warning letters				
OxyContin	1/17/2003	Purdue Pharma L.P.	Pain relief for specific conditions and specific patient populations	Pain relief in a much broader range of conditions and patients with pain
Xeloda	5/29/2003	Hoffmann-La Roche, Inc.	Treatment of certain cases of metastatic colorectal and breast cancer	Treatment of gastric, cervical, uterine, ovarian, renal, bladder, thyroid, and liver cancers
Viread	7/29/2003	Gilead Sciences, Inc.	In combination with other drugs for treatment of Human Immunodeficiency Virus-1 infection	Monotherapy
Pravachol	8/7/2003	Bristol-Myers Squibb Company	Prevention of cardiovascular or coronary events in certain patients, and reducing risk of stroke in patients with clinically evident coronary heart disease	Prevention of stroke in all patients; reducing cholesterol and the risk of cardiovascular outcomes specifically with diabetic patients; and being effective for all patients with borderline-high cholesterol
Diovan	4/21/2004	Novartis Pharmaceuticals Corporation	Treatment of hypertension and heart failure in particular patients	Treatment of patients with type 2 diabetes and hypertension to preserve renal function
Norvir	6/10/2004	Abbott Laboratories	In combination with other drugs for treatment of Human Immunodeficiency Virus-1 infection	Monotherapy and subtherapeutic dosing
Cubicin	8/17/2004	Cubist Pharmaceuticals	Treatment of complicated skin and skin structure infections, not including pneumonia, caused by certain Gram-positive microorganisms	Treatment of all infections, including pneumonia, caused by Staphylococcus aureus
Enbrel	2/18/2005	Amgen, Inc.	Treatment of chronic moderate to severe plaque psoriasis for certain patients	Treatment of milder forms of psoriasis
Tindamax	3/30/2005	Presutti Laboratories, Inc.	Treatment of certain types of trichomoniasis, giardiasis, and amebiasis	Treatment of other types of trichomoniasis and giardiasis, and anaerobic bacteria
Tracleer	7/20/2005	Actelion Pharmaceuticals US, Inc.	Treatment of pulmonary arterial hypertension in particular patient groups	Treatment of pulmonary arterial hypertension in all patient groups
Zyvox	7/20/2005	Pfizer, Inc.	Treatment of nosocomial pneumonia and complicated skin and skin structure infections caused by Staphylococcus aureus or Streptococcus pneumoniae	Treatment of all infections caused by Staphylococcus aureus or Streptococcus pneumoniae

Drug cited	Date of letter	Drug company	Approved condition	Off-label promotion cited
Sotradecol	4/4/2006	Bioniche Pharma Group Limited	Treatment of small uncomplicated varicose veins in particular patients	Treatment of small uncomplicated varicose veins in all patients
Zovirax	6/30/2006	GlaxoSmithKline	Management of initial genital herpes in limited cases	Prevention of transmission of genital herpes
Rythmol SR	9/14/2006	Reliant Pharmaceuticals, Inc.	Treatment to prolong the time to recurrence of symptomatic atrial fibrillation in some patient populations	Treatment of all patients with atrial fibrillation
Orapred	10/11/2006	BioMarin Pharmaceuticals, Inc.	Treatment of severe allergic conditions asthma, intractable to conventional treatment, with asthma or other respiratory diseases	Treatment of all types of asthma
Nevanac	10/20/2006	Alcon Research, Ltd.	Treatment of pain and inflammation from cataract surgery, only involving the anterior portion of the eye	Treatment of ocular conditions in the posterior part of the eye and after any type of eye surgery
Ontak and Targretin	10/23/2006	Ligand Pharmaceuticals, Inc.	Treatment of persistent or recurrent cutaneous T-cell lymphoma in particular patients (Ontak) and treatment of cutaneous manifestations of cutaneous T-cell lymphoma in certain patients (Targretin)[a]	Treatment of T-cell lymphoma in a broader patient population (Ontak and Targretin)[a]
Provigil	2/27/2007	Cephalon, Inc.	Improve wakefulness in patients with excessive sleepiness associated with certain medical conditions; adjunct to standard treatment for Obstructive Sleep Apnea/Hyponea Syndrome	Treatment of various disorders associated with fatigue, sleepiness, or inattentiveness
Ciprodex	4/20/2007	Alcon Laboratories, Inc.	Treatment of acute otitis media and externa caused by certain microorganisms	Treatment of acute otitis media and externa caused by a wider range of microorganisms
Levulan Kerastick	4/20/2007	DUSA Pharmaceuticals, Inc.	Treatment of minimally to moderately thick actinic keratoses of the face or scalp	Treatment of other types of actinic keratosis
Acular LS	5/25/2007	Allergan, Inc.	Solution for the reduction of ocular pain and burning/stinging following corneal refractive surgery	Solution for use in patients undergoing phacoemulsification, a different type of surgery
Exelon	8/8/2007	Novartis Pharmaceuticals Corporation	Treatment of mild to moderate dementia from Alzheimer's	Combination therapy with another product not indicated for same population of Alzheimer's patients

Drug cited	Date of letter	Drug company	Approved condition	Off-label promotion cited
Lindane	12/13/2007	Morton Grove Pharmaceuticals, Inc.	Treatment of head lice, crab lice, and their ova in limited circumstances in particular populations	Dosing claims inconsistent with prescribing information and in broader population
Untitled letters				
Climara	1/6/2003	BERLEX Laboratories, Inc.	Estrogen replacement	For patients with hypertension, hypertriglyceridemia, or gallstones
Quixin	2/20/2003	Santen, Inc.	Treatment of external bacterial eye infections	Prevention of internal eye infections due to eye surgery
Amnesteem	6/18/2003	Genpharm, Inc.	Treatment of severe acne not responsive to conventional therapy	Treatment of psychosocial problems
Flonase	6/19/2003	GlaxoSmithKline	Management of nasal symptoms of rhinitis	Treatment of nonnasal symptoms of rhinitis
Cipro HC and Ciloxan	7/18/2003	Alcon Research, Ltd.	Treatment of eye infections caused by specific microorganisms in the conditions of corneal ulcers and conjunctivitis (Ciloxan)[b]	Treatment of otitis media and otitis externa (Ciloxan)[b]
Merrem I.V.	10/3/2003	AstraZeneca Pharmaceuticals, LP	Treatment of intra-abdominal infections and bacterial meningitis when caused by specific pathogens that are not drug resistant	Treatment of infections caused by particular bacteria and drug-resistant pathogens
Migranal and D.H.E. 45	12/19/2003	Xcel Pharmaceuticals	Acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes (D.H.E. 45)[b]	Treatment of status migrainosis or intractable migraine (D.H.E. 45)[b]
Effexor XR and Effexor	3/18/2004	Wyeth Pharmaceuticals	Treatment of major depressive disorder (Effexor XR)[b]	Treatment of normal periodic feelings of low interest or energy (Effexor XR)[b]
Paxil CR	6/9/2004	GlaxoSmithKline	Treatment of social anxiety disorder	Lesser degrees of performance anxiety or shyness that don't generally require psychopharmacological treatment
Foradil Aerolizer	12/9/2004	Schering Corporation	Long-term maintenance treatment of Chronic Obstructive Pulmonary Disease and asthma that cannot be managed by occasional use of inhaled, short-acting beta2-agonists	Treatment of any type or severity of asthma

Drug cited	Date of letter	Drug company	Approved condition	Off-label promotion cited
Strattera	6/14/2005	Eli Lilly and Company	Treatment of attention deficit/hyperactivity disorder	Treatment of a variety of symptoms, such as disorganization, distraction, and difficulty finishing things
Fuzeon	7/15/2005	Hoffman-La Roche, Inc.	In combination with other drugs for treatment of Human Immunodeficiency Virus-1 infection in certain treatment-experienced patients	Therapy for all treatment-experienced patients
Travatan	9/22/2005	Alcon Research, Ltd.	Reduction of interocular pressure in certain patients	Protection of the visual field
Loprox	1/4/2006	Medicis Pharmaceutical Corp	Topical treatment of seborrheic dermatitis of the scalp in adults	Long-term maintenance treatment of seborrheic dermatitis
NeutroSpec	2/16/2006	Palatin Technologies, Inc.	Diagnostic imaging for assisting in the diagnosis of equivocal appendicitis in patients who are 5 years of age or older	Diagnostic test that can, by itself, diagnose appendicitis
Alimta	7/27/2006	Eli Lilly and Company	Treatment of advanced or metastatic nonsmall lung cancer after prior chemotherapy and in combination with cisplatin for patients with malignant mesothelioma that is unresectable or who are not candidates for curative surgery	Treatment of a wide range of cancers
Rozerem	3/5/2007	Takeda Pharmaceuticals North America, Inc.	Treatment of insomnia, the safety and effectiveness of which in pediatric patients have not been established	Treatment of insomnia in pediatric population
Flonase	5/7/2007	GlaxoSmithKline	Management of nasal symptoms of allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older	Management of nasal symptoms of allergic and nonallergic rhinitis in all populations
Solaraze	7/17/2007	Doak Dermatologics	Topical treatment of actinic keratoses used as monotherapy	Treatment of actinic keratoses in combination with cryotherapy

Source: GAO analysis of FDA regulatory letters.

Note: Regulatory letters are available online from Food and Drug Administration, Center for Drug Evaluation and Research, Warning Letters and Notice of Violation Letters to Pharmaceutical Companies, http://www.fda.gov/cder/warn/ (accessed on Apr. 25, 2008).

[a]In this case, off-label promotional activities were cited for two different drugs. Therefore, information on the approved condition and the off-label promotion cited for both drugs is presented.

[b]In this case, violative promotional activities were cited for two different drugs, but off-label promotion was cited for only one of these drugs. Only information on the approved condition and the off-label promotion cited for that drug is presented.

Appendix II: Examples of Alleged Drug Company Actions Cited in Settlements Involving Off-Label Promotion

Date	Drug company	Drug name	Alleged actions
May 2004	Pfizer, Inc.	Neurontin	• Encouraged sales representatives to provide one-on-one sales pitches to physicians about off-label uses. • Sponsored "independent medical education" events on off-label uses and misled the medical community on the content and lack of independence.
Dec. 2005	Eli Lilly and Company	Evista	• Trained sales representatives to prompt or bait questions by physicians to promote the drug for off-label uses. • Encouraged sales representatives to send medical letters and other marketing materials that were not requested by physicians in order to promote off-label uses.
Oct. 2005	Serono, S.A.	Serostim	• Conspired with a medical device manufacturer to market computer software packages to diagnose AIDS-wasting, although the device was not approved by FDA for this use. The drug company then tried to increase the market for such devices in order to increase the market for the drug. • Offered physicians all-expense paid trip to encourage off-label prescriptions.
Aug. 2006	Schering-Plough Corporation	Temodar and Intron A	• Conspired to make false statements to FDA regarding its improper promotional activity in response to FDA's inquiry regarding certain illegal promotional activities by the company's sales representatives at a national medical conference for oncologists. These false statements were designed to reassure FDA that the promotional activities were isolated and not directed by the home office, when they were actually widespread and part of the national marketing plan.
Oct. 2006	InterMune, Inc.	Actimmune	• Conducted a clinical trial, which failed to establish statistically significant evidence of benefit, but published press releases indicating false outcomes from the clinical trials. • Conducted sales of the drug from August 2002 through January 2003 that were attributable to the prescribing of the drug for the treatment of Idiopathic Pulmonary Fibrosis, an off-label use.
Apr. 2007	Pfizer, Inc.	Genotropin	• Promoted drug for off-label uses, such as anti-aging, cosmetic use, and athletic performance enhancement.
Apr. 2007	Cell Therapeutics, Inc.	Trisenox	• Falsely marketed to physicians by suggesting that it was FDA approved for treating a different type of cancer than approved for, and was listed as medically accepted in the compendia for treating other types of cancers. • Used illegal kickbacks to induce physicians to prescribe the drug and paid them to attend dinners or conferences on off-label uses.
May 2007	Medicis	Loprox	• Targeted pediatricians and urged them to use the drug as a treatment for diaper rash—the drug is approved as a fungicide and not for treating children under 10 years of age.
May 2007	The Purdue Frederick Company	OxyContin	• Promoted the drug as less addictive, less subject to abuse, and less likely to cause withdrawal symptoms than other pain medications without FDA approval.

Date	Drug company	Drug name	Alleged actions
July 2007	Jazz Pharmaceuticals, Inc.	Xyrem	• Made sales calls to physicians, who did not specialize in the area that the drug was approved for, and promoted the drug for off-label treatments and distributed off-label promotional materials. • Paid a psychiatrist to give talks around the country to promote the drug for off-label uses.
Sept. 2007	Bristol-Myers Squibb Company	Abilify	• Promoted the sale of the drug for pediatric use and dementia-related psychosis, both off-label uses.

Source: Compiled from FDA and DOJ sources (www.usdoj.gov and www.fda.gov).

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

DEPARTMENT OF HEALTH & HUMAN SERVICES OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

JUL 11 2008

Marcia Crosse
Director, Health Care
441 G Street NW
U.S. Government Accountability Office
Washington, D.C. 20548

Dear Ms. Crosse:

Enclosed are the Department's comments on the U.S. Government Accountability Office's (GAO) draft report entitled, "Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses"(GAO 08-835).

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

Sincerely,

Jennifer R. Leong for Vincent J. Ventimiglia, Jr.
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED: PRESCRIPTION DRUGS: FDA'S OVERSIGHT OF THE PROMOTION OF DRUGS FOR OFF-LABEL USES (GAO 08-835)

The draft report discusses topics that GAO identified as part of its Congressional request to provide information about the promotion of drugs for off-label uses and recommends a standardized tracking system for DDMAC.

The draft report indicates that reviewers use a process to review submitted materials, but don't apply this process systematically. DDMAC has established documented criteria for reviewers to use in determining how to prioritize their overall workload and which of the thousands of disseminated pieces they receive should be reviewed. The reviewers apply these criteria systematically to all advisory submissions, complaints, labeling reviews, and pending enforcement actions, and actively track all such materials in their assigned therapeutic areas. For submissions of disseminated materials, reviewers consistently apply the documented criteria to determine which of the tens of thousands of pieces received should be reviewed.

FDA, like other regulatory agencies, exercises its discretion in order to focus its limited resources on actions that will most impact the public health. The GAO proposal for a tracking system does not deal with the fact that not all of the approximately 68,000 submitted copies of disseminated pieces received in a year by DDMAC can be reviewed. To address this, FDA established documented criteria to optimally use DDMAC's limited resources. According to these criteria, FDA chooses for review the pieces that raise the most issues in terms of potential public health impact, as described on pages 14-15 of the report – this process represents a systematic prioritization.

This recommended tracking system would also not improve the agency's ability to identify promotional violations, nor would it change which pieces are actually reviewed (with the exception of taking resources away from review activities), as this is determined based on DDMAC's documented criteria. While a tracking system would be of benefit to persons interested in calculating the numbers of pieces looked at, it would not enable DDMAC to more efficiently regulate off-label promotion.

Adding tracking functions to reviewers' current duties would not improve efforts to facilitate identification and review of materials that contain off-label promotion. The agency's limited resources are better spent on substantive review activities aimed at stopping or preventing false and misleading promotion.

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crossem@gao.gov

Acknowledgments

In addition to the contact named above, Geri Redican-Bigott, Assistant Director; Cathy Hamann; Mollie Hertel; Julian Klazkin; Michaela M. Monaghan; and Pauline Seretakis made key contributions to this report.

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