

FDA'S OVERSIGHT OF THE PROMOTION OF DRUGS FOR OFF-LABEL USES

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The Government Accountability Office, GAO, which you may be familiar with, is the investigative arm of Congress and most of our work comes at the request of members of Congress. In July of last year we issued a report on the FDA's oversight of the promotion of drugs for off-label uses. The report originated as a request from Senator Grassley, a Senator from Iowa who is very interested in FDA issues, and who was then the Chair of the Senate Finance Committee.

I know some of this information was covered by the other panelists. I'm going to provide a brief introduction, go through the research questions we tried to answer in our report, how we tried to answer them, provide a little bit of background and then go into our findings.

FDA does not regulate the practice of medicine and recognizes that physicians may determine that prescribing a drug off-label constitutes good care. FDA does not regulate that interaction between doctor and patient. Off-label prescribing occurs frequently, as has been well established from prior panelists. A 2006 study found that more than 20% of prescriptions were in for a hundred of the five hundred most commonly used prescription drugs in the US were for off-label use. Similarly, and it's been going on for quite a while, GAO reported in 1991 that one-third of drug treatments prescribed for cancer patients were for off-label uses, and that more than half of cancer patients received at least one drug for an off-label indication. That being said, it is not permissible for drug companies to promote drugs for off-label uses. That is, for a condition or a patient population for which the drug has not been approved, or in a manner that is inconsistent with the information found in the drug's labeling that has been approved by FDA.

Our report tried to answer two basic questions. The first one, how FDA oversees the promotion of off-label uses of prescription

drugs. The second, what actions have been taken to address these promotions? First, I'm going to explain how we tried to answer these questions. The first question was how FDA oversees the promotion of off-label uses. We interviewed FDA officials from the Division of Drug Marketing, Advertising and Communication, DDMAC is how they refer to themselves, about their review of promotional materials, and their monitoring and surveillance efforts related to off-label promotion. That division is within—Mr. Igoe explained the centers—is within the center of drug evaluation and research within FDA.

Our second question was to determine what actions have been taken as a result of off-label promotion, and we obtained and conducted a content analysis of all 117 regulatory letters FDA issued during calendar years '03 through '07 to answer it. These regulatory letters can take two forms: warning letters or entitled letters. For example, these letters may be in response to a brochure that FDA became aware of or was submitted to FDA. The letter would refer to the brochure, say it was in violation, and ask the company to stop disseminating the brochure and any like materials. This is because often drug companies have promotional campaigns where brochures, posters, and everything that they cite is in violation. The FDA asked them to remove from dissemination. In addition to reviewing for those five years, we also went back to 1997 and looked at all of the violations FDA issued letters for, looking for repeat violations that may have occurred for off-label promotion. We also interviewed officials from other FDA offices, the Office of Chief Counsel, Office of Criminal Investigations. For the second part of the second question we interviewed the HHS Office of Inspector General to determine the settlement piece, which is the table that I handed out, and I'll talk about that later.

So, as for background, after a new drug application and its labeling are approved for marketing, any promotional materials used or distributed by the drug companies must be consistent with and limited to the information on that approved labeling. The Federal Food Drug and Cosmetic Act, in implementing regulations, requires that prescription drug promotional materials not be false or misleading. The regulations state in part that drug promotions may not recommend or suggest any use that is not in the approved labeling. Any approved new drug promoted for an off-label use is considered misbranded.

So we've talked a little bit about what FDA regulates. On this

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slide you'll see a table, I hope you can see, that contains examples of the types of drug company promotions FDA regulates. As you can see, there are printed materials, brochures, magazine ads, and professional journal ads. There's also other media. There's already been some discussion from the panelists on the direct to consumer television ads, websites. The FDA also regulates oral statements, discussions between physicians and drug company representatives in physicians' offices as well as speeches at drug-company sponsored events. I think Professor Byron did a good job of summarizing the recent guidance on the reprints, but just to clarify and reiterate, it only covers reprints of medical journal ads following those guidelines that they laid out, which are very specific. It doesn't include the brochures or magazine advertisements.

The FDA does not generally regulate the exchange of scientific information. For example, information provided at a continuing medical education programs, such as medical conferences and professional gatherings, unless the program has been funded or substantially influenced by the drug company. It is also FDA's position that a drug company may respond to unsolicited requests for information from health care professionals, even if responding means providing information on off-label uses.

So FDA's DDMAC staff oversees prescription drug promotions, which involves reviews of both submitted materials and monitoring and surveillance efforts. There are two types of promotional materials that are submitted to the agency for review. Once a drug is approved for marketing, drug companies are required to submit final promotional materials to FDA on the day they disseminated, so they have that piece to review. They also may voluntarily submit draft promotional materials asking for FDA to comment on if there are any promotions in violation contained in those materials. FDA may provide the drug company with an advisory comment letter stating this brochure is fine or this brochure omits some risk information or contains off-label promotion. DDMAC may also supplement their review of submitted materials with monitoring and surveillance efforts, which includes going to drug company websites or following up on complaints they may receive. Once a violation is identified, DDMAC makes a determination on whether to pursue a regulatory action through a regulatory letter, which I explained is either an untitled letter or a warning letter. A warning letter is a little bit more in depth in that it cites the promotion

violation, requests that the company respond in ten days, and then also requests that the company take corrective action in the same media as the original promotion. Say the promotion is a direct to consumer TV ad. I don't know if you guys have seen, there's a commercial for YAZ birth control where the woman is talking directly to the camera. That would be a corrective action that the FDA negotiated with the drug company and requested that they take. It's been running for quite a while now. So FDA does not have explicit authority to require drug companies to act upon the regulatory letters. However, the agency may initiate enforcement action through DOJ.

Our first finding related to the question of how FDA oversees the promotion of off-label uses of prescription drugs was that FDA's oversight of off-label promotion consists primarily of review of materials submitted by drug companies, but it's unlikely to detect all violations. DDMAC's staff emphasized the review of materials as the best way for them to prevent off-label promotion. They don't have specific staff looking directly for off-label promotions so those reviews occur within the broader review process. So they're looking for a variety of violations, such as omission of risk information, or if they feel the drug company overstated the efficacy of the drug, as well as off-label promotion. DDMAC staff prioritize their reviews because they get a large amount of submitted materials. So for example, an apparent or egregious violation, or a drug that has recently undergone labeling changes, those would be review priorities for the staff.

FDA also engages in monitoring and surveillance. So they do attend medical conferences and go through complaints as a supplement to the review process. Over the years they have received a steadily increasing number of final promotional materials over the five years that we looked at, but they're just not able to get to everything. In addition to not being able to get to everything, they actually don't know what they get to and what they don't get to. DDMAC does not track the number of draft promotional materials it receives for advisory review. They do track how many advisory comment letters they send out, but they don't track how many actual draft promotional materials they receive.

On the other hand, as shown in the previous slide, they track how many final promotional materials they receive at the agency, but they do not track how many they actually review. As for the monitoring and surveillance, it's difficult to identify all off-label

promotion through their monitoring and surveillance. They have a limited staff. They only attend a small number of the thousands of educational programs. And also the nature of that type of promotion, for example oral statements made in the privacy of a physician's office, makes it difficult to identify all violative promotion.

So to answer the question on what actions have been taken to address off-label promotion, we found that regulatory and enforcement actions have been taken in response to off-label promotions. As a result of the content analysis of the 117 letters, we found that forty-two letters cited off-label promotion. That was thirty-six of the total letters in our five-year period. Most of the off-label promotion in those forty-two letters was identified through submitted materials. These were materials that drug companies submitted on the day of dissemination that contained off-label promotion. Digging a little bit deeper into the forty-two letters, 50%—half the promotions cited in the forty-two regulatory letters—were targeted towards physicians and other medical professionals. Thirty-three percent were for both, which included websites, and 17% were consumers only, which we considered to be direct to consumer magazine, television, or radio ads. According to DDMAC officials, in most cases drug companies sent FDA written responses within the ten-day time frame, and ceased dissemination of violative materials. However, there were some occasions that required extensive discussions with drug companies regarding the promotion, especially when they were warning letters and they were required to take some kind of corrective action.

For the second piece of the second finding, we looked at enforcement actions. Between calendar years 2003 and 2007 DOJ enforcement action resulted in 11 settlements with drug companies, which involved, at least partially, allegations of off-label promotion. Some of these settlements involved types of promotional practices most difficult for FDA to identify. In other words, three of them, three of the settlements involved specific allegations of off-label promotion between sales representatives and physicians. Let's talk about a couple of examples. I know Doctor Kane mentioned Neurontin, which was originally approved for anti-seizure use. The alleged off-label promotion was bipolar disorder, pain disorders, ALS, Attention Deficit Disorder, migraines, etc. Some of the specific alleged actions in the settlement were that they encouraged sales representatives

to provide one-on-one sales pitches to physicians about off-label uses and that they sponsored independent medical education events on off-label uses and misled the medical community. Another, more recent example, is in July 2007 with Jazz Pharmaceuticals and Xyrem, which was approved for narcolepsy. They were promoting for alleged off-label uses, which included fatigue, insomnia, chronic pain, weight-loss, depression, and bipolar disorder. That settlement was for \$20 million.

Since the publication of this report there have been more settlements related to off-label promotions. I think we heard from the panelists that Eli Lilly agreed to a total monetary settlement of \$1.4 billion for Zyprexa. That was just recently in January. And there are a lot of other allegations settled in that \$1.4 billion, but a big piece of it was the off-label promotion. Also in September 2008, the pharmaceutical company Cephalon agreed to pay \$425 million for alleged off-label promotion of three drugs; Actiq, GABITRIL and Provigil.

Finally we took a look at DDMAC's action related to the drugs cited in the settlements, and found that they had issued regulatory letters during calendar years 1997 through 2000 for drugs cited in the settlements. Specifically, FDA had identified promotional violations for seven of the twelve drugs in the settlements. Of those seven drugs, drug companies received regulatory letters for five that cited off-label promotions specifically. But only one, and it was TEMODAR, was directly linked to the settlement.

And that concludes my presentation.