New FDA Guidance on Off-Label Promotion Falls Short for Everyone

Obama Administration Is Likely to Revisit It

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The FDA, under President George W. Bush, issued last-minute guidelines that make it easier for pharmaceutical companies to promote "off-label" uses of approved drugs. However, the guidance ignored the entreaties of drug companies to loosen the rules further, and—just to show its even-handedness—rejected requests from P&T committees and public interest groups to tighten those rules. This means that the FDA under President Obama might make some changes outlining what kind of medical journal articles pharmaceutical marketers can distribute to physicians in an effort to convince them to prescribe a drug for an unapproved use.

Off-label promotion is now illegal, but it was allowed by the FDA Modernization Act (FDAMA) of 1996 when companies met certain conditions. That law expired in September 2006. While the law was in force, the FDA never challenged a drug company solely for distributing questionable reprints, according to Richard Samp, Chief Counsel for the Washington Legal Foundation. Claiming that its reprint policies violated the First Amendment rights of drug companies, Mr. Samp sued the FDA. The FDA has levied large fines against drug companies for promoting medications for off-label uses but not for distributing reprints; this is an important distinction.

The Obama administration may want to toughen up the new guidance and, perhaps even more importantly, reverse the Bush FDA's refusal to investigate potential violations and, if necessary, pursue penalities. Certainly, some Democratic constituencies will be pushing the FDA in that direction.

After the guidance was issued, Representative Henry Waxman (D-Calif.), Chairman of the House Energy and Commerce Committee, which oversees the FDA, said, "I hope this policy will be carefully re-examined by the new administration."

Judy Cahill, Executive Director of the Academy of Managed Care Pharmacy (AMCP), feels the same way. She says:

> [The AMCP has] significant concerns about a policy allowing the widespread distribution of such articles. The guidance does not adequately protect against distribution of biased research that would lead prescribers to believe that medications are effective for an unapproved use.

Sarah Donegan, PharmD, Senior Drug Information Analyst in oncology for the American Society of Health-System Pharmacists (ASHP), adds that the best way to distribute off-label information is as part of continuing medical education (CME) programs, in which the information presented must be more carefully balanced.

The guidance, which was published on January 13, 2009, lays out Good Reprint Practice, which summarizes the types of articles and publications that drug companies can pass on to physicians. The idea is to limit reprints to articles in legitimate, peer-reviewed journals that are not funded by drug companies. The articles must be given to a physician separately from other promotional material. They must also contain a prominently displayed and permanent statement disclosing that the uses described in the information have not been approved or cleared by FDA and that there are no ties between the author and the drug manufacturer.

Those and other conditions in the final guidance are similar to the requirements included in the FDAMA exemption except for this important fact: the exemption required companies to submit promotional material to the FDA before distributing it and to apply to the FDA for a supplemental New Drug Application (NDA) for the unapproved use. These two requirements have been eliminated in the new guidance—an omission that has greatly disturbed P&T committees and public interest groups; these groups see the stripped-down guidance as a way for drug companies to sell drugs for unapproved uses without having to go to the expense of submitting an application for approval and thus undergoing the reviews incumbent in that process.

Drug companies take a different view. Genentech, for example, cites its medication rituximab (Rituxan), which the FDA approved in 1997 for CD20-positive, B-cell non-Hodgkin's lymphoma. At the end of 2000, important data on an off-label use of rituximab in diffuse, large B-cell lymphoma (DLBCL) was published in the journal *Blood*. Even though the National Cancer Institute cited rituximab as a treatment option in February 2002 and as the standard of care for DLBCL in August 2002, it took Genentech until 2006 to receive the FDA's approval for that use.

It is this kind of scenario that explains why pharmaceutical manufacturers, especially those offering cancer treatments, pushed hard for the widest berth in the FDA reprint policy. Yet the Bush FDA, which was considered sympathetic to the pharmaceutical industry, stopped well short of giving the industry all it wanted. For example, there is no "safe harbor" in the guidance of January 13, 2009.

Genentech, the Pharmaceutical Research and Manufacturers of America (PhRMA), and the Medical Information Working Group, which is composed of numerous brand-name companies, also wanted the FDA to remove the language in the February 2008 draft guidance. The

guidance had said that article reprints should be based on "adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device."

This is the standard that the FDA has established for clinical trial studies submitted in support of an NDA.

"There are many types of clinically valuable scientific reporting, including case studies, meta-analyses, and observational studies, which may not qualify as 'adequate and well-controlled' under FDA's regulations," PhRMA argued.

In the final guidance, the FDA keeps the "adequate and well controlled" language but genuflects toward the industry. The FDA explains that this research can include historically controlled trials, pharmacokinetic and pharmacodynamic studies, and meta-analyses if the companies are testing a specific clinical hypothesis.

ASHP's Dr. Donegan argues that she would not consider historically controlled, pharmacokinetic, and pharmacodynamic studies to be high-quality clinical investigations. Moreover, the term "adequate and well-controlled clinical investigations" is too subjective for her.

"We wish the FDA [had] defined that much better," she states. ■