More FDA Guidance on Distribution of Reprints

Presenting “New Risk Information” About Drugs

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FDA has long grappled with the thorny issue of the distribution of off-label drug information to physicians by the pharmaceutical industry and has published several draft, final, and revised final guidances related to that issue. The pharma industry and its allies have challenged the FDA’s policies at every stage and fought legal battles in court to defend the right to distribute off-label, but scientifically sound drug information to physicians.

Some Off-Label Litigation History
What is “off-label” drug information? The FDA defines off-label as “use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling.” In the U.S., it is legal for doctors to write off-label prescriptions but until now, it has not been generally legal for pharmaceutical companies to promote any drugs they manufacture for off-label use.

There have been several court cases relating to illegal off-label promotion. The most recent case (U.S. v. Caronia) was a 2-to-1 split decision by the 2nd U.S. Circuit Court of Appeals in New York that threw out the conviction of a sales rep for promoting off-label use of a prescription drug.

The majority decision written by Circuit Judge Denny Chin was based on a Supreme Court ruling that “Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment.” According to Judge Chin, the “pharmaceutical representative’s promotion of an FDA-approved drug’s off-label use is speech” and he was prosecuted “precisely” because of his “speech in aid of pharmaceutical marketing.” Ergo, “we VACATE the judgment of conviction.”

The FDA said that it did “not believe that the Caronia decision will significantly affect the agency’s enforcement of the drug misbranding provisions” of the Federal Food, Drug, and Cosmetic Act. For more on this, see “What’s at Stake in the Off-Label Debate” (http://bit.ly/pmnn11103a).

A String of Off-Label Guidances

That guidance, however, was not well-received by the pharma industry and in February, 2014, the agency released a new draft guidance document entitled “Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices,” which addressed comments from stakeholders regarding the first, “finalized” version.

FDA’s revised guidance was aimed at addressing some of industry’s and the public’s concerns regarding the previous guidelines by making clear that the pharmaceutical and medical device industries can distribute medical and scientific reprints—including reprints of studies for new and unapproved uses of drugs—to medical professionals, but only under certain conditions. Still, the industry was not satisfied.

WLF vs FDA
In public comments submitted to FDA, the Washington Legal Foundation (WLF)—a non-profit legal organization that promotes pro-business and free-market positions—argues that the guidance document is in “direct violation of a 1998 permanent injunction (WLF v. Friedman) it obtained against the agency to prevent it from trampling on industry’s purported First Amendment rights.” WLF said it “intends to enforce its injunction and will seek contempt of court citations against FDA officials who violate its terms.”

WLF cites three FDA proposals with which it has specific issues:

1. FDA proposes that scientific and medical journal articles should be from a peer-reviewed journal, be distributed in unabridged form (i.e. reprint), contain information from an “adequate and well-controlled clinical investigation” and be “scientifically sound.” WLF wants the FDA to eliminate any reference to “adequate and well-controlled clinical investigation,” a reference that, according to the WLF, “likely will be interpreted as imposing severe limitations on the types of journal articles that may be disseminated.”

2. FDA proposes that FDA-approved labeling should be disseminated along with the literature, as well as a comprehensive bibliography of information from other publications (including contradictory literature) and separate from any promotional literature. WLF wants the FDA to narrow the overly burdensome “disclaimer” requirements, such as that the article be accompanied by a comprehensive bibliography and articles/texts expressing contrary or different conclusions.

3. The WLF also wants the FDA to “scale back on the limitations” imposed on disseminating

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medical texts, particularly the distribution of individual chapters from a medical text. “In the absence of such revisions,” says WLF, “it will be virtually impossible for manufacturers to distribute reprints in a manner that complies with the Draft Guidance.”

Pharma Marketing News surveyed readers for their opinions on these and other issues related to the distribution of off-label reprints to physicians by the pharmaceutical industry. Survey respondents were asked their level of agreement or disagreement with the following statements:

A. Under NO circumstances should drug companies be permitted to hand out off-label information—including peer-reviewed journal articles—to physicians and other health care professionals.

B. Doctors have many other sources of information about off-label use of drugs—the Internet and their own journal subscriptions, for example—and do not require that pharmaceutical companies provide this information to them.

C. Limiting reprints to those that contain information from an “adequate and well-controlled clinical investigation” will place “severe limitations on the types of journal articles that may be disseminated.”

D. Requiring a “comprehensive bibliography” to accompany reprints is “overly burdensome” and should be eliminated from the guidance.

E. FDA should “scale back on the limitations” imposed on disseminating medical texts, particularly the distribution of individual chapters from a medical text.

See the results in plotted in Figure 1, below.

Third Time’s the Charm!
On June 6, 2014, FDA issued a THIRD guidance document regarding reprint distribution by pharmaceutical companies: “Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices.” This new document describes FDA’s recommendations for distributing reprints that convey “new risk information” for approved drugs (access the document here: http://1.usa.gov/1qJeynd).

The draft guidance states: “FDA does not intend to object to the distribution of new risk information that rebuts, mitigates, or refines risk information in the approved labeling, and is distributed by a firm in the form of a reprint or digital copy of a published study” if the study or analysis meet specific conditions (see “Criteria of Approved Off-Label Studies”; page 3).

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According to the FDA Law Blog: “The guidance defines ‘new risk information’ as information that becomes available after a drug is marketed that rebuts or mitigates information about a risk already identified in the approved labeling. This term does not include information about a newly identified risk that was not previously included in the approved labeling, or new information that indicates that a risk is more serious than reflected in labeling.”

What about newly identified risk information not included in the label? What about new postmarketing study reprints focusing on efficacy of “approved” uses (as opposed to off-label uses)?

Obviously, the drug industry may not be too interested in distributing reprints that document previously unidentified risk information. Doctors would have to find this information on their own or wait for the FDA to possibly force changes in the labeling, which doctors won’t read anyway.

And if pharma publishes new studies regarding efficacy of approved uses, I’m sure they will want to distribute reprints of those, but only if positive.

What about comparison studies that show the promoted brand drug is no better than older generic drugs? I’m sure those reprints won’t be distributed by pharma sales reps even though FDA may require a bibliography containing all other known studies on the drug (including contradictory ones). Recall that the Washington Legal Foundation wants that out of the previous guidance published in February (op cit).

It seems to me that the FDA is issuing instructions to the drug industry on how to deliver POSITIVE new efficacy and risk data about prescription drugs, not negative data.

Sidney Wolfe Cries Foul!

In a JAMA Internal Medicine viewpoint article published on August 15, 2014, Sidney Wolfe, founder and senior adviser of Public Citizen’s Health Research Group, argues that the draft guidance “suggests that the agency has now tilted toward protecting industry’s commercial speech and away from protecting patients from the risks of prescription drugs and biological products” and would “let the pharmaceutical industry essentially circumvent drug labeling rules and tell doctors that its products have fewer risks than those described in the FDA-approved labeling.”

Does Wolfe have a case?

Wolfe points out that the longer a drug is marketed there is a pattern of new information arising about an increase, not a decrease, in risks and that labeling changes rarely are about reductions in risks. He cites evidence that 15% of drugs approved between 1975 and 2009 received 1 or more boxed warnings and 4% were withdrawn from the market for safety reasons.

An analysis by Eye on FDA blog of FDA warning letters issued since 2004 shows that the drug industry is already prone to underplay the risks of their products in promotions to physicians and consumers (see Figure 2, page 4).

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Wolfe suggests that for FDA to really protect the public health, it should revise its draft guidance to state that when "new information supports a reduction in risk, the company should inform the FDA and provide the evidence, as required under current regulations; if the agency is convinced, the label can be changed. Off-label risk reduction," said Wolfe, "is a misguided approach."