Regulation of Off-Label Drugs Warrants Attention

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PHILADELPHIA — The Food and Drug Administration needs to change the way it regulates promotion of off-label drug use, according to the chair of the department of health policy and public health at the University of the Sciences in Philadelphia.

This year, the FDA issued draft guidance regarding off-label promotion. The draft guidance states that although any materials promoting off-label use must be peer reviewed, approval by the agency is not required, and the pharmaceutical company does not need to prove its intent to submit a new drug application for the off-label use, Robert I. Field, J.D., Ph.D., said at a meeting of the American Society of Law, Medicine, and Ethics. "This is considered to be a significant loosening of the requirements, certainly of the FDA's enforcement attitude."

However, the company must clearly disclose that the suggested use is off-label, and any published negative findings regarding the off-label use must be included in the materials. "The problem is, negative findings don't get published very often, so there's probably not going to be a whole lot of that," he added.

The comment period on the FDA's draft guidance ended several months ago; final guidance has yet to be issued. But there are certainly reasonable arguments for promoting off-label use under certain circumstances, according to Dr. Field.

Medicine only advances when information is shared, "and there are good reasons to allow off-label uses and therefore to allow physicians to know about those off-label uses," he said. "On the other hand, it is clear that lack of oversight will lead to overzealous, aggressive promotion of uses that have limited, if any, scientific substantiation. The big question [is whether the] average physician who's working 80 hours a week [is] really going to be able to evaluate this information, even if it has a disclosure written at the top."

Although the ultimate goal should be to get approval for an off-label use, pharmaceutical companies don't have many good reasons to do so, Dr. Field noted. "The problem is that clinical trials take a lot of time and the FDA is an overburdened agency; its reviews are slow."

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Off-label use is abundant and has increased over the last 3 decades, Dr. Field said.

Before 1997, the FDA opposed all off-label promotion. The agency allowed limited distribution of peer-reviewed articles in direct response to physician requests.

In 1997, Congress passed the Food and Drug Administration Modernization Act, which allowed pharmaceutical companies to initiate distribution of articles promoting off-label use if they came from a legitimate peer-reviewed source, such as a journal or book chapter. Also, companies could sponsor continuing medical education if it was done through a third-party operation.

But there were restrictions on these uses—the material to be distributed first had to be given to the FDA for approval, and the company had to intend to submit a new drug application for the off-label use.

In 1998, the Washington Legal Foundation sued the FDA, arguing that the restrictions on article distribution were unconstitutional under the First Amendment. The court said the agency could limit article distribution but could not require prior submission of the materials for FDA approval or require that the company intend to submit a new drug application. A similar lawsuit in 1999 produced the same result.

These rulings "left questions as to what would and wouldn't be allowed" under the act, Dr. Field said.

Other challenges to off-label promotion rules were not as successful. In 2004, Pfizer Inc. was fined $430 million for paying physicians to promote the off-label use of gabapentin (Neurontin) with little evidence of benefit. And a psychiatrist was arrested in 2006 for accepting $100,000 to promote off-label uses for Jazz Pharmaceutical Inc.'s sodium oxybate (Xyrem). ■