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On the Issues

A Good Framework for Distributing Information on Off-Label Uses

By Scott Gottlieb, M.D.

In this article, AEI resident fellow Scott Gottlieb, M.D., describes how information about a new use of the breast cancer drug Herceptin was slow in reaching oncologists. The Food and Drug Administration (FDA) delayed approving the new indication for almost two years, and during that period, the drug's sponsor could not distribute its findings about the new use. Proposed FDA guidelines on dissemination of information on unapproved uses of medical products, Gottlieb says, will establish a more appropriate standard for what kind of information should be shared.

In early 2005, results of a large, government-run study showed that when the breast cancer drug Herceptin was used after surgery in the treatment of certain early-stage tumors, it could cut patients' chances of relapsing in half. It was a dramatic result. Herceptin, which was developed by Genentech, had been used for years in patients with advanced breast cancers—and with good results. But this was the first significant study to show that when the drug was used in the earlier stages of the disease, its benefits could be even more impressive.

It is rare in the practice of medicine that the introduction of a single treatment can produce such significant benefits relative to its known risks. In breast cancer, perhaps only tamoxifen (administered for five years to patients with estrogen receptor-positive primary breast cancer) produces as significant a reduction in the risk of cancer recurrence. *The New England Journal of Medicine*, in an editorial, called the studies with Herceptin "not evolutionary but revolutionary." The results resonated around the cancer community.

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Immediately after the findings were unveiled at a meeting of cancer doctors in May 2005, prescriptions spiked. But not everyone with early-stage tumors eligible for the drug was receiving it. Even though data showed that wider prescribing of Herceptin would save lives, some oncologists did not immediately embrace the new use.

One reason was the drug's side effects. It caused heart damage in a small number of patients. So there are good reasons why some patients with preexisting heart problems might choose to forgo the therapy. But that alone could not account for all of the underuse. For the vast majority of the 20–30 percent of early-stage breast cancer patients whose tumors express the HER2 protein that Herceptin targets, introducing the drug early in the treatment of their disease—based on the results of the new studies—was a good decision. In fact, today, about 80 percent of eligible women with early-stage breast cancer are getting the drug. That is a penetration rate backed by the science. But in that first year after the results were unveiled, only about 40 percent of eligible women got the drug. The question is why a drug shown to save lives did not quickly win much wider acceptance.

Good Science, Bad Communication

One explanation is that doctors simply were not familiar enough with the new use to embrace it. Even though the results were first published early in 2005, the FDA delayed approving the new indication until November 2006. So for the entire time between the publication of the initial results and FDA approval almost two years later, the drug's sponsor—Genentech—was prohibited from distributing the findings or educating doctors on the new use through sponsored medical education.

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The ensuing information gap probably does not explain all of the underuse, but it surely factors into some of it. Genentech, which has been living under the thumb of the Philadelphia U.S. Attorney's office—which has waged a multiyear investigation into the company's alleged sponsorship of continuing medical education around certain "off-label" uses of its lymphoma drug Rituxan—was not about to risk further legal scrutiny by publicizing the landmark findings with Herceptin.

In the Herceptin case, a failure in communication—and not science—harmed patients. The rapid diffusion of information about new uses of drugs, especially in fast-moving fields of medicine, helps ensure that patients are getting the most up-to-date and effective care. Just as delays in transmitting information about a drug's safety can lead to poorly informed medical decisions, the same phenomenon applies when it comes to information about a drug's effectiveness. In the case of Herceptin, there are women today who will needlessly suffer a relapse of early-stage breast cancer because of nothing more than restrictions placed on the ability of the drug's sponsor to share information about the new use. After all, the drug company is often the only entity with the financial incentive and resources to publicize these kinds of results and individually train doctors on the new use of a drug.

One question, then, is whether the benefits of a strict legal regime—which attempts to restrict sponsors from sharing any off-label information regardless of the clinical circumstances or public health benefits from certain exchanges—are worth the consequences. Inevitably, there will be a lag time between the uptake of a new and important off-label use of a drug and FDA approval of a supplemental new drug application for that same use. The exchange of peer-reviewed literature helps fill that gap in time.

We need to ask whether there are regulatory and legal means to enable a more measured approach to the regulation of promotion that enables distinctions to be made between the sharing of useful information that falls within the bounds of appropriate clinical care versus frivolous information that is well outside of standard medical convention.

Distribution of Valuable and Reliable Information

The FDA's proposed "Guidance for Dissemination of Information on Unapproved Uses of Medical Products" begins to establish a more appropriate standard for what kind of information should be shared. It establishes guidelines under which sponsors can engage in limited distribution of medical or scientific journal articles and reference publications that involve unapproved uses of FDA-approved drugs and medical devices. The publication of these studies in peer-reviewed journals means that they have undergone an evaluation by independent, authoritative clinicians and have been judged to be relevant, truthful, and not misleading. Peer-reviewed publication is recognized as the benchmark in every scientific field for the communication of actionable information. Enabling sponsors to engage in limited distribution of peer-reviewed publications sets a measured standard as to what information could help better inform decisions that doctors make with their patients.

Nonetheless, the publication of the draft guidance has been met with disapproval by critics of pharmaceutical promotion. The reality is that, as a practical matter, the new guidance is likely to have little impact on the actual exchange of off-label information.

Previously, Section 401 of the Food and Drug Administration Modernization Act (FDAMA) set out guidelines that allowed the dissemination of information on unapproved uses of FDA-approved products. As long as the guidelines were met by the manufacturers, the dissemination of such materials was not viewed by the FDA as evidence of "intent" to promote the product for an off-label use. After the courts held that there was a constitutional right to disseminate reprints,

however, many companies shared them even if they were not technically in compliance with Section 401 of FDAMA, which required a pending supplemental new drug application. Section 401 expired September 30, 2006, which is what first prompted the FDA to address this issue in guidance.

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So the reality is that many drug firms went well beyond Section 401 and widely engaged in the distribution of journal reprints, with no consequence. In fact, the FDA—as well as the Justice Department—has stated in the past that they would never bring warnings or prosecutions solely on the basis of dissemination of these reprints. In that regard, the FDA's new guidelines actually establish very specific criteria (for the first time) for the types of journal articles that, as a matter of public health, the agency believes should be eligible for sharing by drug sponsors.

To these ends, the guidelines may actually have the ironic effect of establishing a more restrictive standard than what is commonly practiced. Now that the guidance exists, drug firms are surely going to follow its dictates, since it establishes a de facto safe harbor. But in so doing, they may actually cease to share certain kinds of articles that today would be widely circulated. This might include articles from special supplements or those from journals that do not have clearly established conflict disclosure policies.

So if the guidance is likely to have few practical effects, why did it engender such vigorous condemnation from critics of pharmaceutical promotion? Largely because the document articulates the FDA's belief that certain kinds of off-label information are medically important and relevant for physicians to have access to, even if that means enabling sponsors to share this information. Moreover, the guidance states that there may be circumstances in which the exchange of this information provides public health benefits.

These are views heretical to those who seek strict prohibition of off-label promotion and the imposition of a very narrow legal standard in order to establish efficient tools for limiting off-label sharing. In many cases, these arguments for tight restrictions are driven by anecdotes in which drug firms have crossed conventional boundaries in promoting some drugs for off-label uses that fell well outside medical convention. But a balance can be struck between enabling legitimate information exchange and restricting inappropriate promotion.

As we have seen with Herceptin, not all off-label information and promotional activities are equal when it comes to matters of health. Even stalwart critics of pharmaceutical promotion might be hard-pressed to defend the idea that medical practice in fast-moving fields such as oncology should be defined solely by the information contained within drug labels, and not off-label drug information contained in the medical literature. In fact, more than half of all oncology practice is based on the off-label uses of established chemotherapy drugs.

The FDA guidance sets a science-based standard for sharing credible and relevant information, establishing that studies appearing in medical journals are relevant to the practice of medicine, even in cases where they address off-label uses of approved medicines.

Those who pursue a rigid adherence to restrictions on the exchange of off-label information and who fail to recognize that the sharing of scientific evidence can sometimes have important public health benefits are guilty of pursuing a rigid standard that does not measure the consequences. This standard may provide an efficient way to enforce the law, but establishing the FDA label as the only determinant for acceptable scientific speech loses sight of the fact that these labels are slow to incorporate important medical results about the effectiveness of medical products. They are not the sole basis for medical practice.