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Perspective

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In February 2008, the U.S. Food and Drug Administration (FDA) granted accelerated approval to bevacizumab (Avastin) in combination with paclitaxel as first-line treatment for HER-2 negative metastatic breast cancer. Approval was based on the results of E2100, a cooperative-group randomized trial that showed a 5.5-month increase in progression-free survival associated with the addition of bevacizumab to paclitaxel therapy.[1,2] Confirmatory studies by Genentech, the manufacturer, however, showed that bevacizumab's benefits for progression-free survival may be appreciably smaller than those shown in E2100 and have demonstrated convincingly that the addition of bevacizumab to the chemotherapy agents they have tested offers no increase in overall survival among patients with metastatic breast cancer. As a result, the FDA proposed removing the metastatic breast cancer indication from bevacizumab's label. Genentech filed an opposing petition to request an administrative hearing on the issue (available on the company's Web site, www.gene.com), which is scheduled to begin June 28.

Genentech has a legal right to appeal and request a hearing on scientific grounds, including the possibility that bevacizumab's efficacy depends on the choice of chemotherapy partner or that progression-free survival is a direct rather than surrogate measure of clinical benefit in metastatic breast cancer. Given expert disagreement about how to interpret bevacizumab's performance in the confirmatory trials, a hearing is appropriate to clarify the risks and benefits of the drug. In addition to its scientific claims, however, Genentech advanced four philosophical and political arguments to oppose the FDA's proposed withdrawal of the indication: first, the move has no precedent; second, the possibility of benefit in subgroups of patients justifies continued approval; third, individual patients' choice ought to be paramount; and fourth, the FDA's move will obfuscate the drug-development picture and discourage innovation. In addition, Genentech, claiming that the members of the Oncologic Drugs Advisory

Committee (ODAC) are biased and have inadequate expertise, specifically requested that its hearing be conducted before a different committee.

The precedent for removing bevacizumab's indication is implicit in the U.S. drug regulatory process. Requirements for thorough experimentation undergird that process and modern drug marketing. Phased clinical trials ensure that drugs' safety and efficacy are established with a variety of data from research in humans. These trials also create a public good of vast proportions, since the data are used downstream in prescribing, formulary, and drug-development decisions by actors other than the FDA and the company. This system of experimentation, refined over the past 60 years, depends on the FDA's regulatory authority.[3] The key trigger inducing sponsors to conduct these studies reliably and rigorously is the FDA's veto power over market entry for new drugs or for new indications for previously approved drugs.

Begun in 1992 under Subpart H of the New Drug Regulations, accelerated approval has origins in the scientific and political battles over treatments for HIV–AIDS. The process permits the FDA to grant marketing authorization on the basis of so-called surrogate end points, such as progression-free survival, that are judged reasonably likely to predict clinical improvements in morbidity or mortality. The accelerated approval mechanism thus creates a contract between the FDA and a pharmaceutical company: in return for promises of further clinical studies, the company receives provisional approval and rapid market access. Accelerated approval requires the sponsor to "study the drug further, to verify and describe its clinical benefit," doing so "with due diligence."

Ultimately, data from confirmatory studies should either permit conversion to regular approval or lead to withdrawal of the indication in question. Hence, accelerated approval is provisional — a medium-term stopover en route to full approval or market withdrawal. There should be a clear end point and, after a reasonable period for confirmatory trials, the sponsor should provide evidence that meets the standard for regular approval. If such evidence emerges, the FDA must convert the drug's status to regular approval. Otherwise, the FDA must rescind approval. Without a genuine option to withdraw accelerated approval in light of either inadequate or unfavorable confirmatory data, the FDA would have few tools to ensure that companies provide the new, rigorous data they promised to obtain.[3] Although such adverse decisions may be contested, the integrity of the accelerated approval process and the FDA's reputation and authority as a public health agency require that it be willing to make and adhere to these difficult decisions.

A central question in the bevacizumab dispute concerns whether the standard for conversion of accelerated to regular approval has been met. Genentech argues that progression-free survival is an acceptable measure of direct clinical benefit in metastatic breast cancer and that confirmatory trials demonstrate that bevacizumab prolongs progression-free survival. Yet the progression-free–survival benefit in confirmatory trials, while statistically significant, was considerably smaller than that seen in E2100. In addition, safety concerns — both new and previously described — have arisen from the recent clinical trials.[1,2] Genentech further claims that the FDA has switched approval standards for bevacizumab. The agency, however, has consistently maintained that progression-free survival is "not statistically validated as surrogate for survival in all settings" and is "not precisely measured."[4] Therefore, the FDA has full authority to respond to adverse safety and efficacy data by changing medication labeling.

Genentech's second claim, that the possibility of heterogeneity in the treatment effect should justify continued approval, suffers from an absence of data identifying which patient characteristics are associated with clinical benefit. As the FDA's decision memorandum notes, the mere prospect of efficacy in subgroups of patients, without the ability to identify those subgroups in advance, is inadequate as a rationale for continued approval.

Genentech's philosophical claim that "conflicting interpretations of data should be resolved in favor of retaining access and choice" represents a departure from federal statute and a bold challenge to the FDA's mission. In a democratic republic, access and choice represent two among many values. The FDA must also protect scientific rigor, the integrity and legitimacy of federal regulations and guidance, and the public's health. The agency's reputation

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for using science to guide regulatory decisions in the public interest is its most critical institutional asset.[3]

Genentech's claim that removal of indications from drug labels will chill innovation is unpersuasive. The FDA often removes indications from labeling and commonly rejects new drug applications. Yet there is no consistent evidence that such actions deter the development of clinically valuable therapies. Indeed, the relationship might be the reverse: if bevacizumab offers little promise for patients with metastatic breast cancer, then removing the indication may create a clinical and market niche that provides other companies with an incentive to develop a better product for, or test available products in, that population.

The bevacizumab decision involves not merely the drug but the credibility of the institutions themselves. Underlying the back-and-forth about bevacizumab's trial performance is a larger issue: the precedent that will be established if the FDA reverses its decision on withdrawing bevacizumab's labeling for metastatic breast cancer not because of changing scientific evidence, but in response to philosophical and political counterarguments. As with other FDA labeling decisions, the ultimate outcome in the bevacizumab case is reversible; Genentech remains free to define bevacizumab's efficacy through further studies. If the FDA demonstrates that it is unable or unwilling to withdraw accelerated approval when the totality of evidence fails to meet its standard for regular approval, however, such a precedent risks undermining the basis for accelerated approval mechanisms and, more broadly, the agency's credibility as it seeks to regulate medical products for the public good.

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