THE FDA NIXES A PATHBREAKING DRUG FOR MS

Thirty developed nations have approved Lemtrada. The U.S. refusal to do so shows the need for regulatory reform.

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Alemtuzumab is used today as an intravenous treatment for a form of leukemia. But 20 years of research centered at Cambridge University also has shown that the action of this drug—depleting immune cells that become misdirected and attack one's own body—is effective in treating multiple sclerosis.

Under the brand name Lemtrada (a product of Sanofi and its U.S. subsidiary Genzyme), the drug has been approved in recent months for treating MS in 30 countries, including Canada, Australia and all members of the European Union. But on Dec. 27, Food and Drug Administration reviewers at the division level (subject to a final decision by top officials) rejected an application to use the drug here to combat MS.

We are invested in Lemtrada through a partnership that one of us manages—and we still think the investment will do well. European authorities have called Lemtrada a "step change" in treating MS, and it will promptly become an important therapy at the intermediate "relapsing-remitting" stage of the disease. This is the stage when patients still have periods of normal life before permanent brain and nerve damage sets in.

It was sickening to watch the FDA deny an obviously effective and important therapy to those afflicted with a terrible disease. For as long as the decision stands, much needless suffering will result (and much needless foreign travel). The agency's action is also a vivid example of the serious problems besetting U.S. drug regulation.

The primary reason FDA reviewers gave for rejecting Lemtrada was that the studies demonstrating the drug's efficacy did not conform to the agency's standard requirement of double-blind, placebo-controlled drug trials—where some patients, unbeknownst to themselves and their doctors, receive placebo treatments. There are excellent reasons for the standard approach, but only up to a point. Lemtrada and many established MS treatments have immediate side effects, such as nausea and headaches, that are well known to doctors and patients. A double-blind trial would not really be blind. Patients on a placebo would promptly discover that they were the "controls," and many would decline to participate further—scrambling the statistical comparison with patients receiving real treatments.

The Lemtrada investigators therefore designed "active control" trials that matched it against a leading MS therapy (a branded version of beta interferon) that would be its primary clinical alternative. The trials found that Lemtrada patients relapsed into active MS symptoms at rates 50% lower than patients taking the alternative. These results were buttressed by MRI and other objective measures that found, for example, highly significant reductions in brain atrophy and new brain lesions.

FDA officials turned their backs on these powerful results. Drug regulators inhabit a complex world that mixes strong political pressures, abstract questions of biological science and statistical inference, and practical trade-offs between the benefits and risks of new therapies. In these circumstances, the agency elevated the double-blind, placebo-controlled trial to the level of dogma. It simplifies the reviewers' work and reduces the need to make case-by-case judgments about an appropriate trial design. Most of all, it leaves the agency with wide discretion, at the end of years of development and evidence, to say "no" or "tell us more."

For Lemtrada, the FDA reviewers announced that the trials were not "adequate and well-controlled." They are now demanding another round of trials, with somewhat different procedures, that would take years and cost at least $100 million. Given the magnitude of the results of the already completed trials, the additional trials could add nothing to answering the regulatory question of whether Lemtrada is suitable for clinical use against MS.

The Lemtrada application was one of a growing number of cases where progress in biological science is upsetting FDA doctrine. The drug was developed through decades of "clinical science" that combines scientific method with continuously recalibrated clinical treatments. The research, conducted by world-leading academic neuroscientists, encountered and solved many biological and clinical puzzles along the way, enlarging scientific understanding of MS's underlying mechanisms.

By the time alemtuzumab entered regulatory review, its properties and effectiveness in treating relapsing-remitting stage MS were already well understood. In rejecting a therapy widely known to be highly effective, the agency's reviewers were sending a defiant message to the medical community: The advance of biological research and development must conform to FDA institutional prerogatives rather than the other way around.

FDA reviewers raised an additional concern. Lemtrada, they said, presents serious health risks to patients that may exceed its health benefits. Lemtrada treats aberrations in the immune system, and that intervention does present risks, mainly of thyroid and blood disorders. But the risks of the drug are well known from the Cambridge research and from a decade of clinical use, in much higher doses, treating leukemia. In almost all cases when the disorders do appear, they are much less severe and more easily treated than MS itself.

There is no reason to deny doctors and patients the choice of Lemtrada over other therapies that have risks of their own. For many with MS, the choice will be an easy one—as the fervent petitions of MS patients and advocacy groups during the FDA review attest.

Lemtrada is administered just twice—in one-week intravenous regimens, one year apart—compared with established therapies that are administered continuously on a monthly, weekly or daily basis. And a significant number of Lemtrada patients find themselves free of MS debilities after just the first session. These are enormous benefits. Yet at a public meeting in November, one FDA reviewer warned an agency advisory committee that because Lemtrada patients would have less need to see their physicians constantly, it could be more difficult for physicians and the FDA to monitor them.

This objection is revealing. At some point, regulatory command-and-control needs to make room for the welfare of patients and the skills and professionalism of their doctors.

If Lemtrada does no more than postpone progressive, irreversible paralysis for a few years, permitting patients to live normal lives, that is a great blessing even if some of them fall off the FDA grid. But the therapy is also slowing the progression of the disease—some patients have remained free of clinical disease activity for up to 14 years.

With experience and learning, these successes may point the way to averting MS damage to the central nervous system at the earliest, asymptomatic stages. Medical progress is iterative; it must be free to pursue the logic of the problem at hand at each incremental step.

The cascade of Lemtrada approvals outside the U.S. demonstrates that vigilant public regulation can adapt to, and make use of, modern biological science. It should be adopted here. FDA reform will not be achieved in a single decision, but it will certainly require decisions, and correcting the stark mistake made about Lemtrada would be an excellent step in the right direction.

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