

THE FDA'S DR. NOs

The agency's fear of Type II errors inhibits drug development and harms patients.

◆ BY JOHN J. COHRSEN AND HENRY I. MILLER

The U.S. Food and Drug Administration has a long history of dragging its feet when evaluating badly needed drugs. An extraordinary article last January in the *New York Times* ("F.D.A. Regulator, Widowed by Cancer, Helps Speed Drug Approval," Jan. 2, 2016) revealed how Richard Pazdur, who has headed the agency's oncology drugs group since 1999, was widely viewed as an obstructionist bureaucrat—until his wife developed ovarian cancer in 2012. (She died last November.) Suddenly, Pazdur became a self-described "regulatory advocate" and approval times for cancer drugs have dropped.

Pazdur is one of the legion of "Dr. No's" at the FDA, as described by former National Cancer Institute director Vincent DeVita in his book, *The Death of Cancer* (Sarah Crichton Books, 2015). Their excessive and often capricious interpretation of the new-drug "efficacy" requirement—gauging drugs' effectiveness—lengthens development times and stifles drug research. DeVita points out the paradox that the requirement to demonstrate a new drug's effectiveness was the congressional response to a *safety* (not effectiveness) concern raised by the tragic birth defects caused by the drug thalidomide that was administered to pregnant women in the early 1960s.

The Drug Efficacy Amendment (also called the Kefauver-Harris Amendment) of 1962 added the requirement for proof of efficacy, as determined by "adequate and well-controlled trials," to the criteria for a new drug to be marketed. Ironically, the change would not have prevented the thalidomide tragedy.

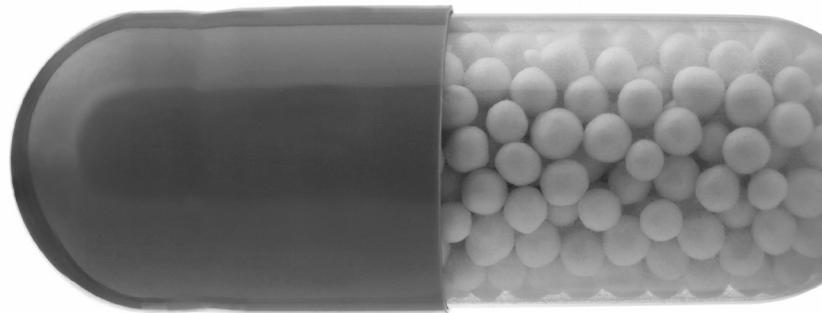
The amendment did not actually require evidence from new *randomized* clinical trials in order for a drug to gain approval. In fact, it mentions using historical controls or data from the natural history of untreated patients to satisfy the efficacy requirement. The requirement for new trials was added by FDA regulations—a power grab by regulators that has expanded with legal require-

ments, if not scientific justification, over the past half-century. As DeVita laments:

Today we seem to be mindlessly wedded to the use of randomized control trials. They have their place. But randomized clinical trials can be unethical.

EVALUATING EFFICACY

The FDA has striven to create an aspirational "gold standard" for drug efficacy. But perhaps counterintuitively, efficacy is a subjective and sometimes elusive construct because drugs can vary in



their effectiveness according to the genetics of the individual treated and the nature and severity of a given patient's disease.

An important factor unrelated to genetics or pathophysiology is the particular way the FDA requires efficacy to be measured and statistically evaluated. Regulators may choose to accept only certain types of evidence—for example, a so-called "double blind" study for a drug (in which neither the investigator nor the patient knows whether the patient is getting an active drug or placebo), instead of simply comparing the test group to historical controls. This choice stands even if it is obvious that treated patients show remarkable benefit and it would arguably be unethical to have an untreated control group.

A critical measure of efficacy in a clinical trial is the "endpoint," the defined goal that the new drug is intended to achieve. Sometimes a "surrogate" endpoint is used as a second-order indicator

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of clinical benefit when a definitive endpoint such as prolonged survival would be impractical. For example, for the prevention of heart disease and stroke, an improvement of patients' blood lipid profile is accepted as an appropriate surrogate and, therefore, an acceptable measure of efficacy.

A subtle point is that the FDA's determination of efficacy does not imply that a drug will work every time or in every patient. A particular drug might work only for a small fraction of patients for a certain indication or condition, while a different drug might work in a different fraction of patients for the same purpose.

Thus, a finding of efficacy in a clinical trial means only that the statistical analysis indicates that the drug has a positive effect overall in the test population. But in individual patients, it might have the desired effect almost always, sometimes, infrequently, or not at all. For example, the widely prescribed blood thinner Plavix works poorly in perhaps nearly a third of the tens of millions of patients who take it because they have a genetic variant of an enzyme that is needed to convert the drug to the active form, and their bodies can't fully activate the drug. But virtually all patients benefit from treatment with certain hormones like insulin and thyroid hormone.

REGULATORS' INCENTIVES

Regulatory decisions are influenced in unobvious ways by various bureaucratic incentives and disincentives. "Gatekeeper" regulators—who must make an affirmative decision about a

propriate anxiety about a new product or technology. These Type II errors are usually a media non-event, eliciting little attention. Drug manufacturers hesitate to antagonize the FDA or alarm investors by making too great a fuss over delayed approvals, and most often comply with the FDA's demands for additional data or jumping through other hoops.

The FDA's bias toward more career-friendly Type II errors has perpetuated the presence of Dr. No's who are reluctant to approve potentially harmful products at almost any cost, and who unnecessarily delay or reject new products of all sorts, including drugs, vaccines, medical devices and even artificial sweeteners and fat substitutes.

A regrettable Type II error is the FDA's recent decision to withhold marketing approval of the new Duchenne muscular dystrophy drug eteplirsen. It follows a revealing demonstration of the FDA's dysfunction during an advisory committee meeting in April. Old-timers can recall an era when the FDA convened experts to supplement the agency's expertise on especially arcane issues of science, medicine, and statistics, and to make recommendations about marketing approval. Now the FDA often orchestrates panels to provide "cover" for its decisions, even framing questions to the committees in ways that nudge them to arrive at a preordained but dubious decision.

The pivotal clinical study on eteplirsen was small and used only historical controls (instead of direct comparison to a placebo or another treatment). But the drug had been shown

to be safe, and effectiveness was evident from the marked improvement in the symptoms of the patients who were treated. Many of the committee members were favorably disposed toward the drug, but the FDA framed questions for the committee in a way that prevented them from voting their convictions. Bruce Ovbiagele, chairman of neurology at the Medical University of South Carolina, voted against approval but said, "Based on all I heard, the

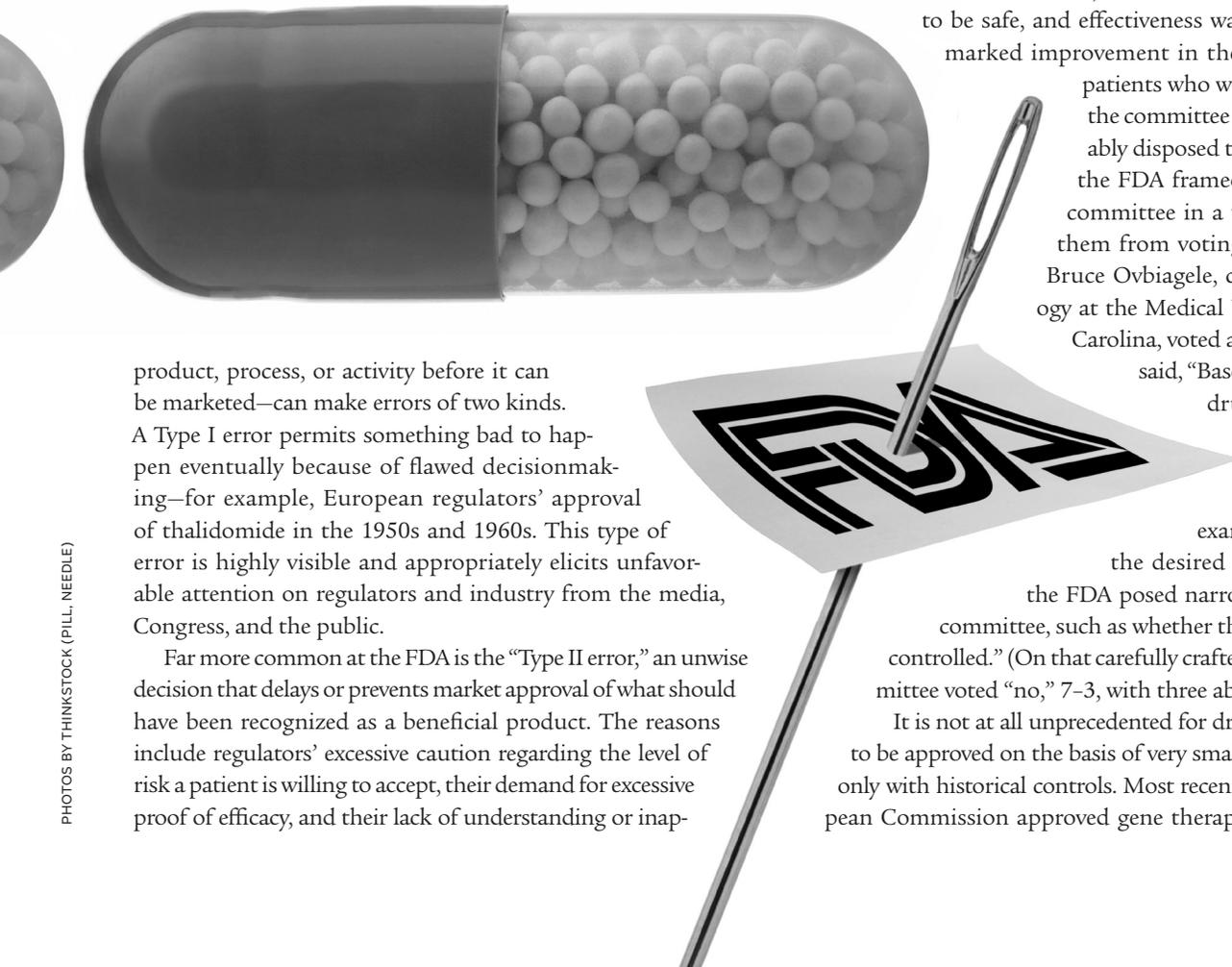
drug definitely works, but *the question was framed differently.*" For

example, in order to get the desired negative responses, the FDA posed narrow questions to the committee, such as whether the studies were "well controlled." (On that carefully crafted question, the committee voted "no," 7-3, with three abstentions.)

It is not at all unprecedented for drugs for rare diseases to be approved on the basis of very small studies performed only with historical controls. Most recently, in May the European Commission approved gene therapy for a rare genetic

product, process, or activity before it can be marketed—can make errors of two kinds. A Type I error permits something bad to happen eventually because of flawed decisionmaking—for example, European regulators' approval of thalidomide in the 1950s and 1960s. This type of error is highly visible and appropriately elicits unfavorable attention on regulators and industry from the media, Congress, and the public.

Far more common at the FDA is the "Type II error," an unwise decision that delays or prevents market approval of what should have been recognized as a beneficial product. The reasons include regulators' excessive caution regarding the level of risk a patient is willing to accept, their demand for excessive proof of efficacy, and their lack of understanding or inap-



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immunological deficiency after clinical trials on only 18 patients (12 in the pivotal study).

REFORM

The tragedy of eteplirsen is not only for the victims of Duchenne muscular dystrophy, but also for victims of other diseases who lack access to promising new medicines when no other treatments are available. They have been victimized not only by illness but also by the FDA's thirst for control, aversion to Type I errors, and disregard for patients' welfare.

This is not a new phenomenon. During the AIDS epidemic of the 1980s, the FDA came under fire and its headquarters were literally stormed by AIDS activists protesting regulators' unwillingness to expedite the availability of new drugs to patients with no alternatives. The frustration of the Reagan administration led Vice President George H.W. Bush to create a blue-ribbon National Committee to Review Current FDA Approval of New Drugs for Cancer and AIDS. The committee presented a report to Bush after he became president, with recommendations that could have eased the FDA's cumbersome regulatory red tape not only for drugs to treat cancer and AIDS, but also other life-threatening illnesses. "Some of the drugs may eventually be found either to be ineffective or to present an unacceptable benefit-risk ratio," the report said, but it also posited that "patients with life-threatening diseases who have no alternative therapy are entitled to make this choice." Patients with AIDS and cancer told the panel that they were "willing to accept this greater risk" in view of the seriousness of the diseases.

The committee's report made clear the extent of over-regulation and offered recommendations to improve the FDA's performance. They included the following concepts, which have not been implemented:

- **New policies.** Using statutory and administrative flexibility, the FDA should approve AIDS and cancer drugs for marketing expeditiously and at the earliest possible point in their development. (We would add to this other experimental drugs for life-threatening illnesses for which there are no alternative treatments.)
- **Structural changes.** Establish an independent Permanent Policy Oversight Committee, reporting directly to the secretary of health and human services, to monitor the FDA's needs and performance with regard to the regulation of drugs and biologics for human use. Also, restructure the FDA advisory committee system so that all committees have their own independent staff located in the Office of the FDA Commissioner, responsible for their own agenda and closely monitoring the progress of the new drug approval system. Finally, solidify close cooperation among the FDA, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases to address issues of clinical endpoints and other drug development/approval problems.
- **Clarify "effectiveness."** The FDA should pay particular

attention to the statutory definition of "substantial evidence" of effectiveness. That definition reflects the intent of Congress that new drugs be approved for marketing on the basis of the scientific judgment of qualified experts that sufficient clinical data exist to demonstrate therapeutic benefit. The FDA should develop and encourage the design of clinical trials to permit widespread access to investigational drugs without sacrificing statistical analysis of drug effectiveness.

- **Institutional review boards.** New drug sponsors should be able to submit proposed Phase I clinical studies to only an institutional review board (IRB) for approval, instead of redundant review by IRBs and the FDA. Phase I and Phase II of noncommercial clinical research aimed at finding new uses for marketed drugs should also be handled through an IRB in lieu of FDA review.
- **Earlier access.** The FDA offers a mechanism—Treatment Investigational New Drug Applications (INDs)—for "expanded access" by large numbers of patients to not-yet-approved drugs. When alternative therapies are unavailable, such applications should be implemented in a flexible way to permit the drugs' use earlier in the development process. Patients should have the right to obtain an investigational drug under expanded-access INDs when there is assurance that clinical trials are under way and will not be compromised.
- **Reimbursement.** The cost of investigational drugs, and marketed drugs prescribed for indications not yet approved, as well as ancillary medical care, should be covered by Medicare, Medicaid, and private insurance, if the use has been approved by expert government agencies, in authoritative medical compendia, or by a committee established by the secretary of health and human services to address these issues.
- **Extra-governmental review.** Sponsors of new drugs should have the option of paying the FDA for outside review of New Drug Applications by qualified experts.

Not surprisingly, FDA officials vigorously resisted the committee's conclusions and recommendations. They claimed the recommendations would diminish the agency's power and reduce the responsibility of drug manufacturers to collect definitive clinical evidence of a drug's effectiveness.

CONCLUSION

A quarter of a century later, the FDA boasts a new generation of Dr. No's who fail to respect the willingness of desperate patients to assume the risks of therapies whose safety and efficacy have not yet been definitively determined. In the absence of such reforms, patients are suffering and dying unnecessarily.

Congress should do what is needed to transform the FDA's Dr. No's into responsible and accountable regulators. Adopting the still-needed recommendations from 25 years ago would be a good start—a boon to patient care and to innovation in drug research and development. R

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