DRUGS AND DEVICE APPROVAL

Patients benefit from the thousands of available pharmaceuticals and medical devices on the market today. But the Food and Drug Administration's (FDA) overly cautious testing and approval process, and demands that such treatments meet a near-perfect level of safety, are often counterproductive. Patients can be injured if the FDA approves a treatment that is later found to be unsafe. But they are also harmed when needed treatments are delayed by regulatory hurdles, or when the cost and complexity of securing approval mean that promising new treatments are never presented for agency evaluation.

Safety concerns that arise after a drug or device is approved result in startling headlines and congressional hearings. That consequence incentivizes FDA regulators to be overly cautious in their decision making, demanding more trials with more patients, raising costs, and prolonging development times. Meanwhile, sick patients who are denied treatment options that may save their lives receive far too little attention. In 2012, Congress required the FDA to more formally measure the life-saving and health-enhancing benefits of new drugs and to explain how it weighed those benefits when making approval decisions. That process should be strengthened and implemented more quickly.

Congress should also require the FDA to update its decades-old rules for testing new drugs. Randomized, placebo-controlled clinical trials are good for detecting when medical interventions have large effects on populations of similar patients. But the homogeneous patient pools and tightly controlled clinical environments associated with randomized trials do not reflect real-world practice and outcomes very well. Existing clinical trial rules do not sufficiently account for variability among patients and differences in patient outcomes that are discovered only after clinical trials are begun. The rules prevent fast-paced adaptive learning in favor of more and longer trials with more patients, even though the latter are ill suited to discovering a drug's safety and benefit profile.

Individual patients disagree about how much risk they are willing to tolerate in order to obtain a new treatment's potential benefits. Therefore, the FDA's one-size-fits-all approval process means that decisions will be too cautious for some and not cautious enough for others. Those who view the agency's approval process as too quick may freely choose to use only products that have been on the market for several years with a well-established record of safety and efficacy. Those who seek access to medical products before the FDA has fully approved them have little or no choice. In theory, the agency's Expanded Access, or "compassionate use," program provides an option for terminally ill patients who cannot be enrolled in a clinical trial to access treatments that have not yet been approved. In practice, however, the process for seeking a compassionate use exemption is complicated, time-consuming, and burdensome, which means that many patients are denied a genuine opportunity to choose.

Benefit-Risk Assessment

The U.S. Food and Drug Administration's statutory mission is to ensure that "substantial evidence" is generated from "adequate and well-controlled investigations" for a new drug's safety and efficacy (21 U.S.C. 355[d], Federal Food Drug, and Cosmetic Act, § 505). But no drug is perfectly safe, in the sense that it has no negative side effects. And each drug affects individual patients differently. So the best we can expect from FDA decision making is a determination that an approved product's benefits outweigh its risks for the typical patient.

Congress should:

- Accelerate the FDA's implementation of the structured benefit-risk assessment process for new drugs mandated by the FDA Safety and Improvement Act of 2012, and require the agency to more fully consider the views of affected patients in approval decisions.

Even after extensive clinical testing, the net effects of a new medicine are not always well characterized. Drugs are generally tested in only a few thousand patients, leaving much unknown at the time an approval or disapproval decision must be made. In practice, the FDA has long been highly cautious when confronted with such uncertainty, even as patients with life-threatening or severely debilitating diseases have expressed a willingness to tolerate greater risk in exchange for the potential benefits of new therapies. Moreover, the agency's process

for assessing and balancing the benefits and risks of medicines is largely ad hoc, informal, and qualitative, relying primarily on the intuitive judgment of its medical review staff and expert advisory committees. As a consequence, agency officials tend to make incompletely informed judgment calls that substitute their own risk aversion for the judgments of affected patients. And because the FDA is not required to explain how it weighs risks and benefits, neither the public nor Congress has sufficient information on which to evaluate the agency's performance.

A 2007 Institute of Medicine report concluded that a more standardized and robust analysis of risks and benefits could improve FDA decision making with attendant improvements for public health. So, as a part of the FDA Safety and Improvement Act of 2012, Congress instructed the agency to "implement a structured risk-benefit assessment framework in the new-drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision making, and the communication of the benefits and risks of new drugs" (Food and Drug Administration Safety and Innovation Act, Public Law 112-144, Section 905). It also instructed the agency to consider in its new-drug approval decisions the views that affected patients themselves place on the value of various benefits and risks associated with new treatment options. However, the statutory text provided no other guidance to the agency, leaving substantial discretion regarding the assessment's structure and implementation.

In 2013, the FDA initiated a five-year plan to develop and implement the risk-benefit assessments, and it has begun to gather information and input from patient organizations to incorporate those views in approval decisions. (See FDA, "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA V Implementation Plan," February 2013, http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf.) Implementation has proceeded very slowly, however, and it remains unclear how the agency will assess the demand by patients for more rapid introduction of innovative treatment options, and what value it will place on those demands. Both the development process and its application to individual approval decisions should be expedited and made more transparent.

Benefit-risk analysis can help decision makers better understand the likely consequences of their actions, and it can lead to greater transparency and accountability by forcing FDA officials to make their assumptions about the value of specific benefits and drawbacks of specific risks explicit. Ultimately, the purpose of formalized and published benefit-risk assessments is to put FDA's expert judgments on record, explain the agency's reasons for approving or denying approval for new products, and hold those decisions up to public scrutiny.

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Clinical Trials

A 2007 report by the U.S. Food and Drug Administration's Science Board concluded that "FDA's evaluation methods have remained largely unchanged over the last half-century," and that "[i]nadequately trained scientists are generally risk-averse, and tend to give no decision, a slow decision or even worse, the wrong decision on regulatory approval or disapproval" (FDA Science Board, "FDA Science and Mission at

Risk: Report of the Subcommittee on Science and Technology," 2007, 3, 5).

Congress should:

- Modernize and streamline the FDA's clinical testing protocols and approval process to take greater advantage of adaptive trial design and active learning.

First developed more than 50 years ago, the FDA's approach to clinical testing—which relies on multiple trials in three phases of testing—is premised on the belief that patients will have similar responses to medical interventions, and that a drug's benefits and side effects will be easy to identify given a large enough test population of patients with similar health and physical characteristics. We now know, however, that similar patients often respond quite differently to the same medications, and that the homogeneous patient pools and tightly controlled clinical environments associated with randomized trials do not reflect real-world practice and outcomes very well.

The FDA's main response to that phenomenon has been to demand more data from more patients to provide greater confidence in its decision making. That approach has caused the length of clinical trials to grow and the median number of tests conducted per patient (such as routine exams, blood tests, and X-rays) to rise. Those new hurdles have also made it more difficult to enroll patients in trials and to keep them in the trials until completion.

Randomized controlled trials are ill suited for detecting and testing subtle differences that occur in small patient subpopulations, which make them poor tools for fast-paced, adaptive learning. To minimize the occurrence of hindsight bias in data analysis, clinical trials begin with a hypothesis and a carefully constructed methodology for testing that hypothesis. When an unexpected or idiosyncratic effect is detected among a subpopulation of the test group, the FDA typically demands that the manufacturer form a new hypothesis and initiate an entirely new, often superfluous trial. In the process, adaptive learning is short-circuited, and the cost of drug development rises still further.

Today, new computational tools, better understanding of disease pathways, the development of biomarkers to predict drug effects, and other technological advances are enabling the use of innovative methods that could improve clinical trial quality. Those tools, combined with adaptive clinical trial designs—which allow researchers to learn as trials are in progress and, in turn, change dosing regimens or isolate patient subpopulations that respond especially well or poorly to the test drug—could help trial sponsors collect better, more robust data from fewer patients and in a shorter time. The FDA has announced its willingness to consider those new methods, but in a way that requires greater testing and more cautious analysis (FDA, "Adaptive Design Clinical Trials for Drugs and Biologics: Draft Guidance," February 2010, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf). If the rules for adaptive trials remain too rigid, they could prevent patients from reaping the full benefits of the innovative methodologies.

The FDA must be more willing to allow flexibility in trial designs and to approve new drugs with fewer trials and fewer patients. Augmenting that accelerated testing process with more robust postapproval monitoring could lead to greater overall patient safety. After all, new drugs are generally tested on only a few thousand patients. The full benefit-risk profile of medicines is often unknown until they have been approved and prescribed to tens of thousands, or millions, of patients in real-world settings. So additional testing before approval simply cannot be expected to reveal a drug's true risks or benefits. Indeed, the rate of drug withdrawals remained essentially unchanged between 1971 and 2004, despite rising and falling trial requirements and approval times during that period. (See Center for Drug Evaluation and Research, "2003 Report to the Nation: Improving Public Health through Human Drugs," Food and Drug Administration, U.S. Department of Health and Human Services, April 23, 2004.)

Since 1992, the FDA has had an "accelerated approval" track for drugs that treat serious conditions for which no other treatments are available. In certain circumstances, such drugs may be granted limited approvals after a single Phase III trial (or on rare occasions, after Phase II trials are complete), under the condition that the manufacturer continue conducting additional trials to demonstrate safety and efficacy. The agency may also designate drugs intended

to treat serious conditions with an unmet medical need as "breakthrough therapies," which may be approved on the basis of a substantial reduction in symptoms or other serious consequences of the disease, rather than evidence that the product cures the disease per se. Those programs have greatly accelerated the introduction of promising new drugs on the market, but the FDA should be more aggressive in combining technologically sophisticated adaptive trial designs with the accelerated approval and breakthrough therapy pathways.

Using aggressive oversight—and, if necessary, additional legislation—Congress should encourage the FDA to permit greater flexibility in clinical trial methodology. It should also encourage the agency to approve drugs sooner and to demand fewer unnecessary trials—substituting more robust post-approval monitoring for the lengthier testing that is unlikely to reveal more about a drug's safety profile.

Expert: Gregory Conko

For Further Reading

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Patient Choice

When making safety evaluations, the U.S. Food and Drug Administration is required, by statute, to determine the appropriate balance between patient safety and medical product effectiveness. The agency cannot know the optimal risk-benefit balance for every patient because each patient will have different views about how much risk and how many side effects he or she is willing to bear in order to use a new treatment that could alleviate symptoms or cure a disease. Therefore, it is important for individual patients to have more opportunities to choose a medical treatment that meets their unique health status and risk tolerance. Currently, few patients ever have the option of choosing a drug or medical device that has not satisfied FDA's risk-benefit preferences.

Congress should:

- Reduce burdens on patients wishing to use FDA's Expanded Access, or "compassionate use," programs and create other opportunities for patients to choose not-yet-approved drugs.

Some patients with unmet medical needs may be eligible to enroll in a clinical trial to test a new medicine or medical device. But because of the need for homogeneous patient populations in clinical trials, many simply do not qualify for enrollment because of their age, comorbidities, prior treatments, and the progression of their disease.

Under current law, the FDA may grant Expanded Access, or so-called compassionate use exemptions, for patients with serious or life-threatening diseases ("Expanded Access to Investigational Drugs for Treatment Use," 21 CFR § 312 Subpart I [2013]). But the process for seeking Expanded Access is complicated and time-consuming. It requires the patient's physician to submit a detailed application, which the FDA estimates will take 100 hours to complete. (See FDA, "IND Applications for Clinical Treatment [Expanded Access]: Overview," October 4, 2013, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm351748.htm; and FDA, "Investigational New Drug Application Form," http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf.)

The manufacturer must also consent to provide the drug, and the paperwork burden for manufacturers is also considerable. In addition, many manufacturers are concerned that granting such access could jeopardize their ability to enroll the clinical

trials needed for FDA approval. And many manufacturers are often reluctant to agree to Expanded Access use, because they may charge patients only the direct costs "incurred by a sponsor that can be specifically and exclusively attributed to providing the drug." (See Food and Drug Administration, "Charging for Investigational Drugs under an Investigational New Drug Application, Final Rule," 74 *Federal Register* 40872, August 13, 2009, http://www.gpo.gov/fdsys/pkg/FR-2009-08-13/pdf/E9-19004.pdf.) The paperwork and resource burden on manufacturers of making experimental drugs available are considerable, and those restrictions often make manufacturers unwilling to participate in compassionate use programs.

Although the FDA does eventually grant nearly all Expanded Access requests that are submitted by patients and manufacturers, that approval often comes many months after applications are submitted, jeopardizing the patient's best opportunity to treat the disease at a stage early enough to be effective. And in the end, the hurdles involved with seeking such an Expanded Access exemption mean that few patients ever even try to use that route. Despite substantial demand for early access to unapproved drugs, only about 1,000 patients each year navigate the process and complete an Expanded Access request.

Individual patients and their doctors are in a far better position than FDA bureaucrats to judge whether the uncertain risk and benefit of new treatments are warranted. The agency should focus on providing them with the information that is, and is not, known about experimental treatments and should permit patients to weigh the potential risks on their own, rather than on restricting patient choice.

Congress has previously examined proposals to reform the Expanded Access process by streamlining the paperwork burden and removing FDA's discretion to deny compassionate use to patients who meet basic qualifications. One such example is the Compassionate Access Act (H.R. 4732), introduced in 2010 by Rep. Diane Watson (D-Calif.). That bill, and others like it, have never reached a floor vote, but they provide Congress with a template to use as the starting point to develop legislation to make it easier for patients to seek and be granted Expanded Access exemptions. In addition, Congress should consider other options for giving patients access to not-yet-approved drugs and devices.

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