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21ST CENTURY CURES: MODERNIZING CLINICAL TRIALS

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Summary of major points

- Congress made the decision that new drugs and high risk medical devices should have their efficacy and safety demonstrated before they could be widely used by patients as a rational response to major public health tragedies caused by the lack of such proof.
- The FDA and Congress have initiated numerous flexibilities to allow the FDA to approve important new drugs on the basis of studies less rigorous than traditional randomized clinical trials testing validated clinical endpoints. These flexibilities shorten premarket testing and regulatory review times and are often employed by the FDA.
- Although the FDA was once considered by some to approve drugs too slowly, drug approvals since 2000 have been quicker in the United States than in Canada or Europe. From 2001 through 2010, the FDA approved 64% of novel therapeutic agents earlier than the European Medicines Agency
- When drugs and high risk medical devices are approved without being subject to rigorous testing, it puts patients at risk. Post-approval study of these drugs is difficult and can be time-consuming. Post-approval surveillance innovations like registries and the Sentinel system are promising but still in active development.



Subcommittee on Health Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee:

My name is Aaron Kesselheim. I am an internal medicine physician, lawyer, and health policy researcher in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham & Women's Hospital in Boston and an Assistant Professor of Medicine at Harvard Medical School. I lead the Program On Regulation, Therapeutics, And Law, an interdisciplinary research core that uses empirical approaches to study intersections between laws and regulations and the development, utilization, and affordability of therapeutics. It is an honor to have the opportunity to share my thoughts with you about modernizing clinical trials and helping expedite access to new prescription drugs and medical devices.

About 50 years ago, Congress made the decision that new drugs should have their efficacy and safety demonstrated before they could be widely used by patients. Congress extended this requirement to a small subset of the highest risk medical devices about a decade later. This wasn't a capricious attempt by legislators to prevent patients from getting the treatments they need, but a rational response by public servants to major public health tragedies caused by the lack of such proof, such as when patients died after taking products with poisonous constituents (sulfanilamide elixir), gave birth to babies with devastating congenital anomalies (thalidomide), or used contraceptive devices that caused bacterial sepsis (Dalkon Shield). In a letter to Congress at the time, President Kennedy highlighted the importance of rigorous testing of new drugs, stating that "[O]ver 20 percent of the new drugs listed since 1956 in the publication *New and Non-Official Drugs* were found, *upon being tested*, to be incapable of



sustaining one or more of their sponsor's claims regarding their therapeutic effect" (emphasis added).¹

When Congress originally gave FDA the power to require new drugs and high risk medical devices to be tested before they could be prescribed to patients, it is worth noting that Congress did not specifically require any particular kind of test. All that is required is that manufacturers provide "substantial evidence that the drug will have the effect it purports or is represented to have," with substantial evidence being defined as "adequate and well-controlled investigations, including clinical investigations." In regulations, the FDA has defined "adequate and well-controlled" as studies having a clear statement of purpose, that permit valid comparison of an experimental and a control group, employ suitable methods to assign study and control groups and otherwise minimize bias, using clear, reliable methods to analyze the study results. These aren't exactly controversial features of a clinical trial. Unfortunately, without the FDA authorized as a gatekeeper in this market, manufacturers of most new drugs and medical devices at the time did not subject their drugs to studies meeting even these minimal criteria, and in the decade after these regulations were first put in place, FDA regulators removed literally hundreds of widely used drugs because they failed to show sufficient evidence of effectiveness upon clinical study.

Generally, the FDA prefers randomized controlled trials, blinded and placebo- or active comparator-controlled, to meet these basic criteria. It is worth recalling that a randomized trial was once an innovation. The requirements for an acceptable randomized clinical trial became recognized and codified slowly over the course of the twentieth century, after decades of debate and consideration leading to consensus about their most important characteristics.² But the FDA



has also recognized that subjecting a new product to rigorous study before approval could prevent timely availability of these products to some patients in life-threatening circumstances. In response, starting informally in the 1970s and spurred on by AIDS activists in the 1980s, the FDA designed the fast track and accelerated approval programs that explicitly permitted truncated pre-market study of drugs and devices for patients with serious or life-threatening conditions. Congress has similarly created special designations for certain drugs and medical devices—using terms such as priority review, orphan drugs, humanitarian devices, and most recently breakthrough drugs—to signal their importance to the FDA. Drugs with these designations are often granted flexibilities in their premarket testing and provided with expedited review by the FDA, and many ultimately receive approval based on uncontrolled studies in small populations rather than randomized trials testing clinical endpoints. As a result, these drugs and devices naturally spend far less time in pre-market development. Fast track, for example, reduced the average clinical development time for a new drug from 8.9 to 6.2 years, whereas drugs benefiting from accelerated approval averaged just 4.2 years. NDA review times have also decreased dramatically, from more than 30 months in the 1980s to 14.5 months by 1997 and to 9.9 months for applications received in 2011.³ We did a study and found that cancer drugs tagged with the “orphan drug” label were overwhelmingly more likely to be tested in methodologically weaker assessments as parts of trials that were more likely to be non-randomized, unblinded, single-arm trials, and/or considered only intermediate surrogate endpoints such as “disease response” rather than survival.⁴ These days, expedited approval programs and special designations have become common at the FDA—in 2012, 26 of the 39 new drugs approved qualified for at least one of these expedited programs. Although the FDA was



once considered by some to approve drugs too slowly, drug approvals since 2000 have been quicker in the US than in Canada or Europe. From 2001 through 2010, the FDA approved 64% of novel therapeutic agents earlier than the European Medicines Agency.⁵

When drugs and high risk medical devices are approved without being subject to rigorous testing, it puts patients at risk. More drugs being approved on the basis of uncertain data will inevitably lead to more drugs being withdrawn from the market after showing safety problems, or weaker-than-expected effectiveness in widespread clinical use. In our study of approved orphan and non-orphan cancer drugs, we found that serious adverse drug events were significantly more likely to occur in orphan drug pivotal trials, as compared with more rigorous pivotal trials of non-orphan drugs. It also creates a conundrum for patients and physicians.

What are physicians supposed to recommend to their patients if the FDA approves a product based on a new clinical trial design that has not yet been confirmed to provide valid data or based on an unvalidated biomarker instead of a real clinical endpoint? Take the case of bedaquiline, a drug for multidrug-resistant tuberculosis approved in 2012 after being granted accelerated approval status, fast track, orphan drug status, and priority review on the way to approval based on two short-term trials testing about 200 patients. In these studies, which were randomized and placebo-controlled, the drug showed efficacy on the questionable surrogate endpoint of converting sputum from *M. tuberculosis* positive to negative. But 2.5 times as many people died from tuberculosis, and 5 times as many people died overall, in the bedaquiline group than in the control group.⁶ Patients with tuberculosis want to be cured – they don't want to die with cleaner sputum. Should physicians withhold prescribing bedaquiline until greater scientific certainty is achieved? How do patients and individual physicians make sound risk-benefit determinations



about this drug in the absence of conventional scientific data? How should physicians weigh the fact that these new drugs will be phenomenally expensive and many patients' insurance companies may require substantial cost-sharing on the part of patients?

The prospect of approving more drugs based on innovative trial designs that diverge from traditional randomized trials puts greater pressure on the post-approval drug and device surveillance systems and the conduct of confirmatory clinical trials. Studies show that manufacturers' commitments to continue studying drugs after approval may be delayed or incomplete. In addition, once a drug is FDA approved for a certain indication, convincing patients to subject themselves to further randomized trials of a drug for that indication can be challenging, because patients can receive the drug directly outside the trial. This will frustrate the medical community's ability to gather the very confirmatory evidence that may be desired. It is perhaps no wonder that the FDA gave the makers of bedaquiline until 2022 to complete confirmatory clinical trial data on the drug's effectiveness in tuberculosis. Systematic screening for safety issues through the Sentinel initiative or medical device registries shows promise, but these efforts are still relatively novel and researchers like the ones in my Division at Brigham and Women's Hospital are still working out the proper methods to make sure the safety surveillance can be accomplished in a reliable manner.

In summary, the prospect that researchers may be able to design new ways of conducting clinical trials of investigational drugs is exciting, and I hope that the best of these truncated designs are indeed proven to work and provide the same level of confidence as standard randomized trials. Increasing the efficiency of drug development is an important goal.

However, the FDA already has the flexibility in its laws and regulations to integrate validated



innovative study designs and validated biomarkers into its review process. Indeed, the FDA already exercises this flexibility to remarkable extent, providing numerous pathways for important new drugs treating unmet medical needs to be approved in a timely manner on the basis of single-arm, uncontrolled, unblinded trials when necessary. If regulators and others in the medical community are still skeptical about certain biomarkers and clinical trial designs, it's probably because the science supporting them is still in its infancy, in which case forcing approval of the drugs or devices to which they are applied would be dangerous for patients and problematic for physicians.



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