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FEATURE

FDA unease about faster drug approval

A little noticed FDA report reveals internal opposition to Trump plans to speed drugs to market. **Peter Doshi** looks at its arguments

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Days before Donald Trump took office, the Food and Drug Administration quietly released a report[1] that reads as both a forceful defense of large randomized trials and a plea to save such "phase III clinical trial" testing requirements—arguably the most distinctive feature of drug regulation over the past half century—from extinction.

For an agency that marks each drug approval decision with a celebratory press release but generally does not publicly announce even the name of applications it rejects—the report is a surprisingly thorough compilation of 22 specific case studies of drugs, vaccines, and medical devices. In each case, the product showed promising results in phase II studies but failed to shine in phase III trials—and ultimately was not approved for the intended indication (box 1, table 1⇓).

In the words of the unnamed authors of the FDA report, "Phase 3 trials help care providers understand when a medical product provides clinical benefit to patients that outweigh the risks. … As we continue to explore alternatives to requiring phase 3 testing, it is important to keep in mind the benefits they provide to both patients and to the medical research enterprise."

It takes little imagination to see why the report may have been difficult to publish under a Trump administration. Among the contenders for the FDA's top job was Jim O'Neill, a Silicon Valley investor who had previously served in the Department of Health and Human Services as principal associate deputy secretary. O'Neill was widely criticized for having no medical background, and the media focused on a hitherto little known speech he made in 2014 that suggested an interest in eliminating phase III testing.[3]

"We should reform FDA so that it is approving drugs after their sponsors have demonstrated safety, and let people start using them, at their own risk, but not much risk of safety. But let's prove efficacy after they've been legalized," he said.

John Powers, professor of clinical medicine at George Washington University School of Medicine and Analysis adviser for The BMJ, rejects this proposition. Safety, Powers says, is not the absence of harm but "a balance of efficacy compared to harms of drugs. Since all drugs have side effects, if a drug does not work to improve how patients feel, function, or survive, it cannot be safe." Phase III studies, which evaluate drug efficacy on patient outcomes, fill this void. "The law in the US since 1962, reinforced by court decisions, has required evidence of efficacy specifically in order to evaluate 'safety.' Demonstrating efficacy is not an option that can be discarded based on personal policy positions or beliefs," he says.

Efficacy not borne out

The FDA report tells the story of bitopertin, a drug that Hoffman-La Roche hoped to market for add-on treatment of schizophrenia. The drug passed through animal studies and phase I testing in humans and, in the words of an editorialist, "represents the culmination of more than two decades of basic and clinical research on the glutamatergic model of schizophrenia."[4] Authors of an eight week phase II study of 323 patients reported a statistically significant 25% reduction in negative symptoms versus placebo in the per-protocol population.[5] But by the time that trial was published, its sponsor had declared the results of phase III testing. Three double blind studies enrolling over 1800 patients with follow-up of at least one year did not reproduce the encouraging phase II results, with two failing to demonstrate efficacy.

False sense of safety

But perhaps a more troubling aspect of the report—particularly for those who believe that a drug's harms can be fully described by the time it enters phase III studies[6]—are the many stories of safety problems that emerged in phase III studies. Novo Nordisk, for example, hoped to market a form of recombinant activated factor VII (rFVIIa) for acute intracerebral hemorrhage. A phase III study, investigators reported, was done "to confirm a previous study in which [rFVIIa] reduced growth of the hematoma and improved survival and functional outcomes."[7] But instead of confirming the phase II results, the phase III study showed a lack of clinical benefit and an increase in thromboembolic events compared with placebo.

Such cases, says Jeffrey Aronson, a clinical pharmacologist at Oxford University's Centre for Evidence Based Medicine, "demonstrate the danger of forgoing phase III studies, without which there is a high risk of missing serious adverse reactions. Carefully controlled phase III studies are, or should be, designed to detect not only benefits but also harms and to estimate the benefit to harm balance before medicines are licensed. After marketing, many patients will be exposed in uncontrolled

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Box 1: Understanding phase I, II, and III trials[1 2]

To gain regulatory approval, most drugs and biological products must successfully complete a series of clinical trials broadly classified in three phases:

Phase I studies—First test of a product in humans, usually healthy volunteers. Trials are generally short and aim to gain a rudimentary understanding of how the product interacts with the body. Multiple doses of a product are tested to learn about acute toxicity, and the information is used to help design phase II studies

Phase 2 studies are generally larger and longer than phase I studies. Participants have the disease or condition the product aims to treat or prevent. Efficacy and adverse event data are collected to help develop hypotheses for testing and determine whether the balance of benefit to harm is sufficient to justify phase III studies. Phase II studies often measure only laboratory values or biomarkers and are generally too small to confirm efficacy on patient centered outcomes or delineate adverse effects

Phase III studies tend to be both larger and longer than phase II studies, which helps rule out chance findings and allows sufficient time to observe the effect of the product on patients' lives (how they feel, function, or survive). Phase III studies aim to confirm efficacy in people with the target disease. These trials generally assess clinical outcomes and gather more information on adverse events to determine if and how the product can be used to ensure benefits outweigh harms.

fashion and may suffer harms that would otherwise have been detected in phase III."

Indeed the report, given its focus, omits the many products that were withdrawn for safety reasons despite being approved after phase III studies, such as rofecoxib, cerivastatin, and temafloxacin.

Tip of the iceberg?

The 22 cases presented in the report may be far from an exhaustive list. The FDA, which does not disclose information about unapproved indications, limited its report to cases that could be documented using publicly available sources such as sponsor press releases and journal articles. The authors write that the selected cases were "chosen from a large pool of similar examples." Furthermore, they note that the unexpected results in phase III trials occurred in a wide range of circumstances: from acute to chronic conditions, both common and rare diseases, and for preventive measures such as vaccines as well as for treatments.

FDA under Scott Gottlieb

Although many may have worried about the demise of phase III studies under an FDA headed by Jim O'Neill, last month the White House announced it had chosen Scott Gottlieb for the job.[8]

Gottlieb is presently a venture partner at New Enterprise Associates and resident fellow of the American Enterprise Institute think tank, with longstanding ties to the pharmaceutical industry.[8] He has served in various capacities in the FDA, including deputy commissioner under President George W Bush, when he recused himself from decisions involving nine companies, according to *Time Magazine*.[9] Today, he has links to about 20 healthcare companies.[10]

Gottlieb is known for an interest in streamlining and speeding the drug approval process, consistent with Trump's deregulatory agenda.

"We're gonna be cutting regulations [at the FDA] at a level that nobody's ever seen before and we're going to have tremendous protection for the people, maybe more protection for the people," Trump told a group of drug company executives in January.[11] "You're gonna get your products either approved or not approved, but it's gonna be a quick process. It's not gonna take 15 years." (It should be noted that FDA reviews generally take under a year; 15 years may refer to pharmaceutical development time.)

Joel Lexchin, a professor emeritus at York University who researches drug safety, says Trump "is off in fantasy land" in linking drastic cuts in regulation to improved safety. Lexchin has highlighted the dangers of speeding drugs to market[12] and notes: "There is already a large amount of evidence that links faster drug review times to more safety problems once drugs are available for sale. Couple faster approval times with less evidence and a less rigorous evaluation of that evidence and it's quite probable that you'll get a sharp uptick in safety problems with no accompanying benefits." Research has already linked drug review deadlines with safety problems.[13]

But Gottlieb, like Trump, often depicts regulation as a hindrance to improving public health[14] and has defended industry's rights to First Amendment protection.[15] He has also called on the FDA to be more transparent about its reasons for disapproval of drugs by publishing so called "complete response letters," generally treated as confidential.[16]

Surrogate markers

One mechanism many expect the FDA to use to speed decisions is a heavier reliance on surrogate endpoints—for example, laboratory measurements intended to predict clinical benefit. Gottlieb, who was the overwhelming industry favorite for the job,[17] has criticized FDA decisions in which the agency required evidence of clinical benefit before approving a drug, arguing the agency should have instead relied on a surrogate endpoint.[18] Gottlieb says the agency's evidentiary requirements are too high for rare diseases and supported the 21st Century Cures legislation (which passed under the Obama administration) that calls on the FDA to make greater use of surrogate measures.

In his advocacy work, Gottlieb has for years cited the case of a drug for Hunter's syndrome in which he argues regulators should have known to trust a surrogate measure because of the drug's action in related diseases. Instead, the FDA required a placebo controlled trial showing clinical benefit.[19] "Needless to say, the drug proved highly effective," Gottlieb wrote.[18]

The FDA report on 22 case studies, however, though primarily concerned with a defense of phase III trials, also includes a strong rebuttal to Gottlieb's portrayal of the power of surrogate endpoints.

"While biomarkers have many important uses in clinical practice and product testing, most have not been shown to reliably predict clinical outcomes." They cite six cases, noting that "promising biomarker data in phase II do not necessarily translate into effective product performance." One such case was torcetrapib, a drug Pfizer called the "most important new development in cardiovascular medicine in years."[20] Phase II studies had shown that it increased "good" high density lipoprotein cholesterol levels and lowered "bad" low density lipoprotein cholesterol. A phase III study confirmed these findings. But Pfizer ended its development program after another phase III study with over 15 000 participants found that those receiving torcetrapib "were 25% more likely to suffer a major adverse cardiac event, and

were 58% more likely to die from any cause," than those taking placebo. Both results were statistically significant.

Joseph Ross, associate professor of medicine at Yale University, concurs with the FDA report, noting that though some surrogate markers, such as viral load for HIV therapies, have proved reliable, many others are problematic. "Those used for regulatory approval of therapies for diabetes, cardiovascular disease, cancer, and many more have only been found to be weakly, or even not all, predictive of clinical outcomes after further study. If the FDA is going to continue to allow regulatory approval based on trials using surrogate markers of disease, there must be strong post-market requirements placed on manufacturers to complete studies that use clinical outcomes in order to ensure the clinical community understands the true benefits and risks of any approved therapy," he says.

The report also casts doubt on projecting clinical benefit from a product's apparent mechanism of action: "There was a plausible mechanism of action associated with most products in these case studies, but that often did not translate into clinical benefit."

Wither phase III studies?

On the same day he tendered his resignation, FDA commissioner Robert Califf published a Viewpoint in *JAMA* on the core task of the FDA review process: determining whether "the benefits of a product outweigh the risks when used as intended and labeled?"[21]

Citing the FDA's then just published report, Califf wrote: "The history of evidence generation for medical product development shows that benefit and risk cannot be accurately predicted without objective data gathered from well-designed clinical trials ... Even when early data are promising, well-designed trials often return surprising results, namely that the product is not effective or causes harm."

It is far from clear whether new leadership at the FDA will retain an equally cautious approach.

Competing interests: See http://www.bmj.com/about-bmj/editorial-staff/peter-doshi. In addition, PD has coauthored research with John Powers.

Provenance and peer review: Commissioned; not externally peer reviewed.

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Table

Table 1| 22 case studies of products that fell at phase III trials1

Product	Purpose	Reason for refusal (lack of)*
Aliskiren	Add-on treatment to prevent complications of congestive heart failure	Efficacy
Bitopertin	Add-on treatment for schizophrenia	Efficacy
Brivanib	Hepatocellular cancer	Efficacy
Capsaicin topical patch	HIV associated nerve pain	Efficacy
CoSTAR drug eluting stent	Reduction of risk of myocardial infarction in patients with coronary artery disease	Efficacy and safety
Darapladib	Prevention of cardiovascular disease complications in patients who have had myocardial infarction	Efficacy
Dexmecamylamine	Add-on treatment of depression	Efficacy
Exhale drug eluting stent	Reduction of shortness of breath in patients with emphysema	Efficacy
Experimental HSV-2 vaccine	Prevention of genital herpes	Efficacy
Figitumumab	Advanced non-small cell lung cancer	Efficacy and safety
Glutamic acid decarboxylase vaccine	Preservation of insulin secretion in patients with recent onset type 1 diabetes	Efficacy
Imiquimod	Molluscum contagiosum lesions	Efficacy
Iniparib	Add-on treatment for “triple negative” breast cancers	Efficacy
Lithium	Delay disease progression in amyotrophic lateral sclerosis	Efficacy
MAGE-A3 vaccine	Treatment of non-small cell lung cancer after surgery	Efficacy
NicVAX vaccine	Smoking cessation	Efficacy
Olanzapine pamoate	Long acting treatment for schizophrenia	Safety
Recombinant factor VIIa	Reduction of intracerebral bleeding and hematoma size in patients with stroke	Efficacy and safety
Semagacestat	Improvement of cognitive and functional status in Alzheimer’s disease	Efficacy and safety
Torcetrapib	Prevention of cardiovascular disease events in patients with a history of cardiovascular disease or type 2 diabetes	Efficacy and safety
V710 vaccine	Prevent *Staphylococcus aureus* infection	Efficacy and safety
Velimogene aliplasmid	Metastatic melanoma	Efficacy

*Lack of safety denotes adverse effects in phase III trials were substantial enough to change balance of harm and benefit.