



Testimony before the Committee on Oversight and Government Reform
Subcommittee on Energy Policy, Health Care and Entitlements

United States House of Representatives

“FDA Checkup: Drug Development and Manufacturing Challenges”
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Mr. Chairman, Mr. Ranking Member:

Thank you for the opportunity to testify today before the Committee on Oversight and Government Reform, Subcommittee on Energy Policy, Health Care and Entitlements.

My name is Scott Gottlieb. I am a physician and resident fellow at the American Enterprise Institute. I previously worked at the Food and Drug Administration as the agency's Deputy Commissioner and at the Centers for Medicare and Medicaid Services as a senior advisor to the Administrator during implementation of the Medicare Modernization Act.

I am on the policy advisory boards to the Society of Hospitalist Medicine and the Leukemia and Lymphoma Society; and a member of the advisory board to the National Coalition for Cancer Survivorship. I am presently a Clinical Assistant Professor at the New York University School of Medicine. I remain active in the capital markets related to healthcare, and I am closely engaged with a number of the life science and healthcare services companies through a variety of consulting relationships and board assignments. I am here today testifying in my capacity as a Resident Fellow at AEI, and as a physician.

I want to address today the issues related to FDA's review and approval of novel treatments for serious diseases that aren't adequately addressed by available medicine.

The FDA has been effectively implementing provisions included in the last reauthorization of the Prescription Drug User Fee Act related to "Breakthrough" therapies that target these kinds of conditions. I believe these provisions are having a noticeable impact on FDA's willingness to embrace new approaches to expedite the development of these sort of therapies, and to take a more balanced approach toward weighing risk and benefit in these settings.

But I still believe there is more that can be done. That the drug development process itself has become needlessly long and costly owing to regulation that serves to add to pre-market burdens without meaningfully improving the safety of drugs (or what we know about their effectiveness). And that we're not taking full advantage of what science has made available, not only in terms of new and more targeted therapies, but better ways for evaluating them.

First on what we have recently achieved: To date, it's my understanding that FDA has received 90 Breakthrough designation requests, the agency has designated 30 products, and has approved three drugs that were labeled breakthrough therapies. All of these have been products from FDA's drug center. FDA's Biologics Center has approved none of the 10 requests it has received, to date, seeking "Breakthrough" therapy designation.

In my view, the breakthrough therapies authority has had a tangible impact on the drug center. It has enabled a re-examination of how the center handles priority applications for novel and promising drugs aimed at unmet conditions. It has enabled senior management in the drug center to play a more hands on role in helping to shape the policy and regulatory requirements around very novel areas of drug development -- concepts like targeted

therapies, genetically targeted drugs, and drug and diagnostic combinations. It has reinvigorated provisions that have long been in place to allow FDA added flexibility to expedite the development and review of promising therapies. These provisions such as accelerated approval have been marginalized in recent years as FDA backed away from the spirit, if not the letter of the prior statutory language that created these pathways.

The “Breakthroughs” designation has allowed these old concepts to be dusted off.

But there is more that needs to be done when it comes to how FDA handles the development of drugs aimed at unmet needs. The fact is that a lot of the most significant FDA challenges aren’t problems with regulation or statute. They are issues of culture.

The review staff at FDA is a dedicated and well-intentioned clinical group of people who are often leading experts in their respective fields. But they are also heavily influenced by outside voices – and it’s often the critics that are talking the loudest.

Years of complaints about the agency’s oversight of drug safety, about the high cost of drugs relative to their perceived benefits at the time of initial market entry, and criticism about the science that FDA uses in its review processes from vocal academics who often have their own, parochial views on these matters – all of these things have all taken a toll on the culture of FDA. Over time, it is sanding down people’s willingness to take the risk of adopting new approaches to the agency’s work, even around areas of unmet medical needs that might not have had anything to do with the concerns that incited the initial criticism.

The result is that a fear of uncertainty now pervades the review process. This fear is so pervasive that it impacts not only the assumptions FDA is willing to make about a new drug’s safety, but also its efficacy. When it comes to drugs targeted to unmet medical needs, I believe it’s a fear of uncertainty around efficacy that is having the most burdensome impact on how drugs are being developed. FDA staff is often unwilling to take any risk when it comes to their observations around drug efficacy. They require experiments that leave little or no doubt that the magnitude of the benefit being observed in a trial is not a function of any statistical chance, or of a problem with how the trial was constructed or conducted.

In short, they want to conduct pristine experiments that leave little doubt that the results describing a drug’s efficacy are precise and beyond any statistical doubt.

Here it is important to distinguish between the magnitude of the benefit being observed, and the believability of that result. I am not talking here about FDA’s concern that a drug must show a certain amount of benefit. Some threshold of measurable benefit is always necessary to provide a proper balance against known risks. Judging how much benefit can offset a given risk in a particular condition is a matter of judgment, and a policy call.

Rather, it’s how FDA guarantees the believability of that observation of benefit that I believe is having the most significant delay on the development of new drugs.

To illustrate these issues for an article I published in the journal *National Affairs*, I turned to the recent history with the development and approval of drugs to treat a family of inherited

inborn errors of metabolism called mucopolysaccharide (MPS) diseases. I want to return to this narrative here, and briefly expand on it, to illustrate my point.

These diseases are a large group of metabolic disorders caused by the absence or malfunctioning of certain enzymes (called lysosomal enzymes) that are needed to break down certain sugar molecules found in the blood, called glycosaminoglycans. Since the body is unable to properly break down these sugar molecules, they end up building up in vital organs – with painful, debilitating, and often deadly consequences.

Many of these diseases are extremely rare. Since all of them are inherited, they start to affect people when they are typically very young. These diseases often claim the lives of their victims early. These disorders comprise a group of more than 40 genetic conditions. Some of these different disorders are so rare, that they affect as just a few hundred patients worldwide.

As I noted in National Affairs, drugs that could function as replacements for the missing enzymes have been developed for a number of these diseases, demonstrating that if the enzyme could be effectively reproduced, and delivered to patients in a way that enabled it to get to the target organs, then it would deliver a benefit to patients. Through these approvals, the basis for understanding how a replacement enzyme could function as a treatment in one of these related disorders has been firmly established over a period of more than a decade.

Yet an unfortunate thing happened as each of these similar enzyme replacement drugs -- for one of these closely related diseases -- came before FDA. With each approval, the agency's requirements for the next drug got more demanding, not less, even though the theoretical basis for understanding how these enzyme replacements worked was being more firmly established. This was so, even though each of these diseases was distinct, meaning an enzyme replacement approved for one disease – although conceptually very similar to the enzyme approved for another disease – still wouldn't work on the related disorders.

In short, when it came to these drugs and these diseases, the FDA was not using its accumulating experience with the success of prior enzyme-replacement drugs to streamline its evolving process. Instead, it was making it more and more cumbersome.

As I noted in National Affairs, the first drug to treat one of these disorders was Ceredase, which was indicated for Gaucher disease, a genetic disorder that kills most affected children before the age of five. The FDA approved Ceredase in 1991 on the basis of a single, six-month study of 12 patients; when regulators saw that the livers and spleens of these patients were shrinking, the FDA took this as evidence that the replacement enzyme was having its intended clinical benefit. If the FDA had required statistically significant evidence that the drug enabled patients to function better or live longer, rather than settling for proof that it addressed the physical markers of the disease, the trial could have taken several years.

Drugs were developed for several more of these lysosomal storage disorders. With each approval, the requirements FDA imposed on the next drug grew more burdensome.

By the time a drug for another one of these diseases, Hunter Syndrome, came before the agency in 2003, FDA's standards had grown substantially. Even as the agency became more

aware of how these drugs functioned, and delivered their benefits, it used its accumulating knowledge not to streamline the development of the next drug, but make it more difficult.

In order to approve the drug for Hunter Syndrome, the FDA required the trial to involve 96 patients with Hunter syndrome — some 20% of all Americans afflicted with the disease. Moreover, for the first time in such a study of enzyme-replacement therapy, the FDA also insisted that patients be randomly assigned to receive either the experimental drug or an inert placebo. The course of Hunter syndrome follows a regular pattern in most afflicted children; the results for patients who got the experimental therapy could easily have been compared against readily available historical databases that track the normal course of the disease. As I noted in *National Affairs*, it's hard to see why a placebo was necessary in such circumstances, especially when the requirement for a placebo group meant that some of the kids involved wasted a full year of the most able portion of their short lives effectively going untreated.

FDA also required a “clinical” endpoint in this trial — a measure that the drug was improving the function of the children, and not just impacting a “surrogate” measure of benefit, like shrinking their enlarged organs. In this case the two measures FDA chose were the ability to walk and breath (through the use of a “walk test” and pulmonary function tests). These and several other requirements meant that the Elaprase trial took longer, and was costlier, than any previous trial involving similar drugs. Prior trials with drugs targeting one of these rare enzyme disorders had lasted six months or less. The Elaprase trial, by contrast, was designed to last at least a full year. And all that time, the parents, the doctors, and the children did not know if they were getting the new drug or the useless placebo.

Unfortunately, the agency's history with how it handled the review and approval of drugs for these MPS diseases is a familiar one. It's not that the clinicians who work on these reviews are unaware of the suffering caused by these and similar diseases. They want to see new, effective treatments delivered to patients. They are aware that clinical trials like the one demanded for Elaprase can impose extraordinary hardships on patients and their families.

But simply put, there is a tradeoff that has become too commonplace in how we develop drugs. This tradeoff is a view that, in the long run, society will benefit more from a regulatory process that demands the development of very precise information about a new drug's benefit up front, before the drug is approved, rather than a process that enables timelier access to these treatments.

There is a view that if precise information isn't developed prior to approval, it will never accrue to medicine. This is simply not true.

And there's a view that sacrificing timelier access to a new drug for today's patients, and imposing even significant hardships on patients in clinical trials in the present time, will benefit many more patients in the long run by forcing the creation of better information.

I don't believe this tradeoff is appropriate, or necessary. I believe there are ways to enable faster development of new drugs for unmet diseases, and timelier access, while still ensuring that future patients will have appropriate information on which to base decisions.

But FDA, left to its own discretion, will always have a preference for designing experiments that leave little doubt about the magnitude of a new drug's benefits, and therefore leave the agency with a relatively easy decision when it comes to its review process and its decision to approve or reject a new drug. These ideal experiments, however, come at a significant human cost, not just in terms of time, but also money. They create barriers to investment in new treatments. And they make the development process much longer than it needs to be.

It's this desire to reduce uncertainty about efficacy (as opposed to just a focus on drug safety) that I believe is the most significant issue in delaying access to new drugs targeted to unmet needs. In many cases, when it comes to the newer, more targeted drugs aimed at rare diseases, safety is not the most prominent question. The safety profiles of these treatments are fairly well understood. Most often, the regulatory issues turn on a question of efficacy, and the desire of FDA to make sure that it has firmly established, with statistical precision, the full magnitude of the observed benefits. When we are dealing with diseases that affect very few patients, this imperative for exactitude can demand enormous costs and hardships.

FDA points to its review times and often argues that there are no problems with how it is handling applications for the vast majority of drugs. The cancer division at FDA routinely publishes these results, with self-congratulatory commentary about the timeliness of their reviews. The agency does deserve some credit here. Once an application is submitted to FDA, especially for drugs aimed at unmet needs, they typically undergo a timely review. The cancer division has done some very fast reviews in recent years. But I believe these statistics are, in some ways, misleading. They don't reveal the whole story on what is unfolding.

Now surely if the review times were long, that would invite criticism. But at the same time, the fact that FDA can lay claim to review times that are, on average, commensurate with review times in Europe, ignores the most important aspects of enabling timely access to new therapies. It's everything that happens before an application is submitted to FDA for review that counts most. It is all the time taken developing the drug that really counts. FDA can make rapid review of applications because the development programs are so exhaustive that they yield clinical data that speaks for itself – the review decision is made readily apparent.

For this reason, the ease of FDA review is often inversely proportional to the cost of development. The biggest chunk of time between the discovery of a new compound in the laboratory, and its approval as a new drug, is not spent while the application is under review at FDA. It's spent while the compound is undergoing the traditional three phases of clinical trials to satisfy FDA's review requirements. The more data generated during this process (and the more statistical rigor demanded of that evidence) the easier the job that FDA has reviewing the final results. This creates a strong incentive for FDA to impose substantial requirements when it comes to how those trials are conducted. That's what is happening.

It's these requirements that are raising costs, expanding development timelines, and creating a significant barrier to the entry of new medicines. By most estimates, the total average development time for a new drug is 15 years, at a cost of more than \$1 billion.

So how can we build on the success of the "Breakthrough" therapies pathway, to continue to improve the process for how FDA directs the development of drugs targeted to serious conditions, and goes about reviewing the results of these clinical trials?

We need to focus on reforms that will help the review culture at FDA evolve when it comes to these issues. I want to offer some suggestions that are aimed toward these ends.

First, we should consider changing how clinical effectiveness is defined in the setting of rare diseases. FDA insists that there is a single standard for establishing “safety and effectiveness.” But the agency already maintains (and sometimes uses) enormous latitude in adapting its clinical requirements based on circumstances. I don’t believe that simply giving FDA more flexibility to streamline its pre-market requirements in certain settings is going to appreciably change how the agency approaches these challenges. It has that flexibility right now.

Instead, I think the FDA needs much clearer direction around when we, as a society, want it to exercise that discretion. To these ends, the Europeans have a much more explicit pathway that allows the limited approval (for a five year period) of drugs that show activity against very vexing disorders, but have not firmly established the same level of statistical proof of benefit as required for more common medicines aimed at more routine conditions.

This doesn’t mean that safety and effectiveness isn’t firmly established for the drugs aimed at rarer disorders. It only means that we are making a much more explicit acknowledgement of a virtue that’s already embedded in the discretion that FDA sometimes exercises – that the clinical trial requirements for demonstrating proof of benefit are not fixed, but adjust based on the circumstances. Vexing diseases like Gaucher’s sometimes demands that FDA embrace a less certain standard for statistical conviction in order to expedite a new drug.

We might consider some statutory changes that could hasten this sort of change. For example, hardwiring into statute language that already exists in regulation that enables FDA to use a standard that relies on a single clinical trial or a surrogate measure of benefit when it comes to certain unmet diseases – changing language that says FDA “may” to FDA “shall.”

Second, the breakthrough therapies pathway has been a successful legislative effort and its implementation by FDA has had a palpable impact on the review process. But a full-throated embrace of the spirit of this legislation requires a cultural change at FDA that is invariably slow to unfold. For these reasons, we might consider also changing the organizational structure of FDA to hasten the adoption of these kinds of provisions.

Specifically, rather than allow drugs aimed at very rare or serious disorders to be reviewed alongside drugs targeted to more common maladies (and more conventional development programs) we might consider carving out the novel drugs for more serious conditions into a separate group inside FDA – a sort of “skunk works” charged with implementing novel review requirements and regulatory science aimed at expediting the development of critical medicines. There are many new, and effective regulatory concepts that could streamline the development process, making it more efficient and perhaps more effective.

There’s no reason FDA’s review process has to be strictly organized only by clinical areas. Most of the consultants to the review process are already therapeutic generalists who work across multiple areas. A separate group charged with managing “Breakthrough” applications could maintain its own clinical experts, or borrow them on consult from the divisions.

What ideas might such a group more readily embrace?

Concepts that can change how we develop drugs, introducing greater efficiency – ideas like the use of adaptive trial designs, Bayesian statistical techniques (rather than the more traditional, frequentist approach to statistical design), and wider use of molecular profiling and targeting of medicines. These are not new concepts. But they are very slow to gain any level of adoption. In an agency where reviewers are under constant political pressure and time constraints, they don't feel a lot of liberty to incorporate unfamiliar and new approaches, or take new risks in embracing concepts that are untried. So they stick with familiar constructs, even if these traditional approaches are unnecessarily costly or burdensome.

A separate group that's appropriately staffed with people expert in these new methods could help advance not only the development of very important drugs, but also the science behind FDA's regulation. The counter argument to carving out these "Breakthrough" applications is that the existing review divisions need to be challenged with these new concepts. But it's going to continue to be hard for the existing review teams to both meet current deadlines and demands, while trying to take some measure of risk with new approaches. It's time to consider placing the task of exercising these new authorities like "Breakthroughs," and developing the science behind these new approaches, in a separate team inside FDA that's charged daily with thinking about how to do things differently.

These are just a few ideas on how to advance FDA's science, and make the process for the consideration of drugs aimed at vexing and unmet diseases more efficient. FDA has made great strides towards these ends through its recent implementation of the "Breakthrough" therapies pathway. I would argue that to make further and more significant reforms, it would require measures that start to change the culture of FDA as it relates to these challenges.

These goals can't be accomplished through statutory or regulatory language alone. Lasting change requires a change in FDA's mindset, and its tolerance for risk and uncertainty.