Changing the FDA's Culture

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Hunter syndrome is a terrible disease that cripples, and often kills, children. The illness robs its victims of the ability to produce a crucial enzyme used by the body to break down certain sugar molecules that are found in vital organs. In Hunter-syndrome patients, these molecules accumulate in places like the heart, brain, and joints with debilitating and extremely painful consequences. The disease is genetically inherited and very rare: At any given time, there are only about 2,000 cases worldwide. Before a treatment came along, parents had to stand idly by and watch as the disease destroyed their children.

By the 1990s, however, there was cause for optimism. Drugs were developed that could function as replacements for the enzymes missing because of Hunter syndrome and a series of related rare disorders called lysosomal diseases. By 2004, the Food and Drug Administration had approved enzyme replacements for four conditions very similar to Hunter syndrome; patients using these drugs were seeing promising results. The basis for understanding how to treat these genetic disorders was firmly established: If scientists could replace the missing enzymes in the blood, then the advance of these diseases could be slowed. In some cases, the damaging effects could even be partially reversed. The drugs were helping patients live longer, less painful lives.

When an experimental enzyme-replacement drug for Hunter syndrome came along a decade ago, parents of children with the disorder were understandably desperate to get their kids the new medicine, called Elaprase. Many families traveled hundreds of miles so that their children could take part in the drug’s key clinical trial. They may have

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expected that the trial would be an example of effective regulation hastening the timely arrival of a safe, new treatment. Instead, what these families experienced exemplified a broken and dysfunctional approach to drug trials, driven by an FDA culture poorly suited to serving the needs of the sickest patients.

In an effort to satisfy an increasingly unreasonable hunger for statistical certainty on the part of the FDA, the trial imposed extraordinary hardships on the children and families involved. In order to approve the drug for use, 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 is well documented and follows a very 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. It is 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.

These and several other requirements meant that the Elaprase trial took longer, and was far more complex and difficult, than trials of similar drugs in the past, thus delaying the drug’s approval. Previous 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. To make matters worse, only a small number of doctors treated Hunter syndrome, so there were not many sites around the country that participated in the clinical trial. This meant that many parents had to travel long distances so that their children could get the required weekly doses. 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. By the time the trial was finished, if Elaprase worked (as was widely expected), many of the children who had been put on the placebo would be crippled.

The story of the Elaprase trial is important not because it stands out as an exception, but rather because it is increasingly characteristic of the FDA’s drug-review culture. That culture is the product of a poorly understood, but now well-established, attitude within the agency: an excessive desire for certainty. This desire is primarily driven not by fear
of unforeseen dangerous side effects caused by drugs under review, but rather by a deepening mistrust of the doctors who eventually prescribe such medicines and the companies that market them. And that mistrust, in turn, is impeding the availability of safe, effective drugs that could today be helping real patients.

Fortunately, however, this harmful culture can be readily improved—by implementing a few straightforward reforms of the FDA’s responsibilities and structure.

A Culture of Mistrust

Many observers quite plausibly trace the origin of the modern FDA review process to the 1960s and the public-health tragedy caused by the drug thalidomide. In that dreadful episode, thousands of women (mostly in Europe) had been prescribed thalidomide for morning sickness; the drug, it turned out, arrested the limb formation of babies during the early stages of pregnancy. This was before the era of ultrasounds, so it was not until babies were born months later—with ghastly birth defects—that the full magnitude of the drug’s toxicity was discovered. Though thalidomide had been approved for sale in Europe, it was held up in the United States precisely over safety concerns that, clearly, were well founded. The FDA reviewer who delayed the drug’s approval in the U.S., Frances Kelsey, became something of a national hero, and was given the President’s Award for Distinguished Federal Civilian Service by President John Kennedy.

The episode had a lasting effect on the FDA’s work. First, it led to the passage of the Drug Efficacy Amendment in 1962, a new law that created the modern clinical-trial requirements. An equally important development, however, was the way in which the thalidomide episode transformed the FDA’s review culture. It fostered an idealization of the lone reviewer championing an issue of safety against the prevailing orthodoxies, especially when it meant taking on corporate interests. Every FDA reviewer wanted to be the next Frances Kelsey. To this day, the thalidomide episode influences the agency’s staff; in 2010, the FDA created an annual Kelsey award for a staffer who tilts against standard conventions.

The thalidomide episode also had a more subtle influence on the way the FDA goes about its work: It focused the agency’s attention on a certain category of risks in which the problems are latent, meaning they do not become manifest until many months, and perhaps years, after exposure to a drug. Particularly prominent among such dangers are the
risk of birth defects (teratogenicity) and of cancer (carcinogenicity). In the years since the thalidomide episode, the FDA has become extremely proficient at uncovering these kinds of delayed side effects.

This is more or less how the FDA understands its own review culture— as devoted to averting risks and protecting the public, and as being very good at doing so. This devotion comes with some downsides, to be sure: In so heavily prioritizing one of its obligations—the protection of consumers—the FDA has sometimes subordinated and neglected its other key obligation, which is to guide new medical innovations to market. Even now, many FDA employees see these two roles as fundamentally in conflict, despite the fact that the timely approval of effective, life-improving, and life-saving drugs is also a big part of the agency’s responsibility. But on the whole, the agency’s reviewers believe it is appropriate to prioritize safety over speed.

The trouble is that another set of priorities, motivated by another set of transformative events, has shaped the FDA review culture just as profoundly, but in ways that have not been adequately noticed or acknowledged. To truly understand today’s FDA review culture, we must look past the thalidomide tragedy to another (and much more recent) episode involving drug safety. During one relatively brief period in the 1990s, there were suddenly reasons to question the safety of four FDA-approved drugs: the diabetes medicine Rezulin, the antibiotic Trovan, the pain drug Duract, and the bowel drug Lotronex. The clinical problems caused by these four new drugs, the ways in which these problems were managed by doctors, and the political pressure applied to the FDA as a consequence combined to dramatically alter how the agency understood its mission.

Each of these drugs followed a remarkably similar path, which is best illustrated by the story of Rezulin—the incident that had the greatest direct impact on the FDA’s review culture, and the one that came to embody that entire difficult period in the agency’s history. Rezulin was part of a new class of oral treatments for diabetics who could not easily use insulin; hailed as a major breakthrough, the drug was the first entirely new treatment for diabetes in decades. But shortly after its approval in 1997, a small number of patients started to develop serious liver damage. It became clear that, in rare cases, Rezulin caused an extremely serious drug-induced form of liver failure.

As the number of Rezulin users who went on to suffer acute liver failure began to mount, the FDA instructed the drug’s manufacturer to issue
“Dear Healthcare Professional” letters to all American physicians. The letters informed doctors of steps they should take to mitigate the risks associated with Rezulin, and reminded physicians to prescribe the drug only to patients who had exhausted other, more common treatment options. The letters also directed doctors to use routine blood tests in order to closely monitor the liver function of patients on the drug.

In the FDA’s view, doctors failed to heed these clear warnings and instructions, and continued to prescribe the drug to patients who were at risk of experiencing Rezulin-related liver problems or who did not need the drug in the first place. And data clearly showed that physicians were not taking the FDA’s advice about monitoring liver function. By the spring of 2000, 94 cases of Rezulin-linked liver failure had been reported. Many of those patients required liver transplants to save their lives, and some died as a result of the liver failure.

The impact of the Rezulin episode on the FDA’s review culture was reinforced by similar problems with Lotronex, Duract, and Trovan in the very same period. Taken together, these incidents transformed the FDA’s relationship with doctors and medical practitioners. The agency’s senior management and staff lost trust in physicians — especially primary-care doctors — and came to believe that doctors could not be relied upon to read drug labels and heed clear FDA warnings.

FDA staff began to argue that the only way to ensure the safe prescription of drugs was to regulate physicians directly. But as Murray Lumpkin — then the FDA physician in charge of the agency’s drug-safety office — warned, the agency had no such direct regulatory authority. Moreover, restrictions on doctors’ prescribing could be hard to enforce. “If we’re getting to a point where we’re getting a standard of drug approval that says we can only approve drugs after we have second-guessed how they will be misused and how to keep the misuse from happening,” Lumpkin cautioned, “that’s going to be a very difficult standard.” The head of the FDA’s drug-review center, Janet Woodcock, echoed those sentiments: Once a drug is proven effective and safe, she said at the time, the FDA depends on doctors “to take into account the risks, to read the label…. We have to rely on the practitioner community to be the learned intermediary. That’s why drugs are prescription drugs.”

But as the safety problems with Rezulin and other drugs caused public and political pressure on the FDA to mount, the agency’s views changed. “As medical practice has changed… it’s just much more
difficult for [doctors] to manage” the expanded drug supply, Woodcock said in an interview with the *Los Angeles Times* in the summer of 2000. “They rely upon us much more to make sure the drugs are safe.” Shortly thereafter, the FDA tried to get the legal authority to regulate how certain drugs would be prescribed; FDA staff wanted to be able to place direct restrictions on doctors as a way for the agency to more closely manage how the riskiest drugs would be used.

The FDA got some of that authority through the FDA Amendments Act, which was enacted in 2007. The law allowed the agency to put into effect “elements to assure safe use,” which required doctors to take certain steps — such as undergoing special training or running certain tests on patients — before they could be allowed to prescribe drugs that the agency deemed especially risky.

Yet even these new authorities have proved insufficient to assuage the agency’s concerns. The FDA still has very limited ability to counteract the will of doctors and patients who do not always agree with the agency’s judgments. And it is in an effort to work around these limitations that the FDA requires an extraordinary degree of certainty in drug trials — even in cases where speed is of the essence.

**THE NEED FOR CERTAINTY**

This hunger for extreme certainty about how drugs work — born of an inability to trust doctors to do their jobs — is essential to understanding the FDA’s evolving approach to drug trials. The agency’s concern is not chiefly that a new drug will go on to have some serious side effect that agency staff failed to discover before approval; the modern FDA is exceedingly good at unearthing common, and even remote, risks. Rather, the FDA’s main fear has to do with the question of a drug’s “effectiveness.” In the specific case of Elaprase, for instance, the reviewers were worried about the risk that the trial results would leave some doubt about the drug’s efficacy in different circumstances — and so leave doctors unsure of exactly how to prescribe and employ it.

This fear flows from a presumption among review staff that the FDA is the lone bulwark standing between truth and chaos when it comes to prescribing drugs. Reviewers believe that if the FDA does not use its approval process to coerce reluctant sponsors into constructing exhaustive studies — studies that extract every single kernel of potentially relevant clinical information — then no one will ever adequately mine
these data. And because physicians cannot be fully trusted to do their jobs without this information, and companies can’t be trusted to market drugs responsibly, the FDA believes, the delays caused by collecting such extensive data in prolonged trials are worthwhile.

There is, of course, no shortage of anecdotes regarding bad doctors and unscrupulous drug-marketing practices that reviewers cite to substantiate these concerns. Litigation and FDA investigations over the past several decades have revealed that dozens of drug companies engaged in illegal, off-label promotion of drugs, and that a smaller number of companies engaged in illegal and insidious kickback schemes to compensate doctors for prescribing certain medicines. One of the most celebrated cases involved the drug company TAP Pharmaceutical, which settled charges in 2001 that it had conspired with doctors to enable them to book fraudulent payments for prescribing the company’s prostate-cancer drug Lupron.

From this experience emerges the FDA’s sense of obligation to regulate not only drugs, but also how they are prescribed. Indeed, in recent years, the FDA has rejected drugs that the agency felt were perfectly fine for the uses for which they were intended; in each case, the deal-breaker was agency staff’s fears about how the drug might be prescribed “off label” for medical indications for which FDA staff did not think the benefits justified the risks. The painkiller Arcoxia fell into this trap: The drug was rejected in April 2007 because of the concern that it could increase the risk of heart attack and stroke with prolonged use. But the drug was meant for short-term pain relief, and could have been clearly marked and described as such. The FDA did not trust doctors to reliably prescribe the drug for only short periods of time, and to only those patients who had tried other painkillers to no avail.

Simply put, the modern FDA is driven by a profound lack of confidence in the ability of doctors to make careful judgments. The agency regulates drug makers, but it does not regulate doctors: The actual practice of medicine is supposed to be regulated by state governments. And while drug labels and other materials made available to physicians provide a great deal of information about the approved uses of prescription drugs, doctors are permitted to use their judgment when prescribing. They are not always required to strictly follow labels or FDA directives.

There is a powerful sense inside the FDA today that, once a new drug is approved for one narrow purpose, poorly informed doctors
manipulated by drug marketing will prescribe it for all manner of ailments—even while lacking a clear understanding of the potential consequences. Many agency reviewers are specialists who have a particularly dim view of primary-care doctors, and it is primary-care doctors who do most prescribing.

Precisely these reservations about the competency of practicing physicians drive the trend toward increasingly demanding drug-trial requirements, and in turn are responsible for the fact that trials continue to get longer, larger, and harder to enroll. In 1999, drug makers had to perform a median of 96 procedures on patients enrolled in trials, collecting data through measures such as x-rays and blood draws. By 2005, the number of tests performed on each patient grew to a median of 158. During the same period, the average length of a clinical trial stretched dramatically—from 460 days in 1999 to 780 days in 2005. Given that these increases impose enormous burdens on trial participants and cause delays in the approval of life-saving drugs, they are a very costly way for the FDA to assuage its mistrust of the medical profession and its practitioners.

**Escalating Barriers**

To understand just how harmful this lack of trust is to the cause of medical innovation, it is helpful to return to the Elaprase trial and related drug approvals as a case study. Indeed, the story of the gradual development and approval of the series of enzyme-replacement treatments that preceded the Elaprase trial offers an especially clarifying example of the FDA’s evolving attitude toward doctors, clinical certainty, and the tradeoffs between protecting against doctor error and allowing the development of life-saving drugs.

This story begins in a place of relative medical certainty: The basis for understanding how a replacement enzyme could improve the lives of patients with a rare disorder like Hunter syndrome had been well established by the time Elaprase was submitted to the FDA for approval. Nevertheless, as each new replacement enzyme that targeted one of the related disorders was reviewed and approved by the FDA, agency staff increased the hurdles that the next drug had to clear, rather than lowering them. The FDA was not using its accumulating experience with the success of these enzyme-replacement drugs to streamline the process. Instead, it was making it more and more cumbersome.
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. Ceredase was approved by the FDA 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 it 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. But given the severity of the disease, as well as the absence of alternative treatments, the agency opted to approve Ceredase once the drug’s safety was clearly established.

There was a downside to Ceredase, however: It was derived from human placental tissue, leaving a theoretical risk that the drug could transmit viral infections—a particularly pressing concern in the heyday of the HIV epidemic. So in 1994, when a synthetic version of the same enzyme was developed, it was viewed as a welcome breakthrough. But during this next review process—for the new synthetic version of the drug, called Cerezyme—the FDA required the drug to be tested in 30 patients for approval. That sounds like a small study, but it is a lot of patients to test when dealing with a disease that affects fewer than 2,500 Americans.

More recently, in February 2010, when the FDA approved an upgraded version of this replacement enzyme, the agency required the drug to be tested in 99 patients. It also wanted the drug (named VPRIV) to be tested in some patients who had not received any prior treatment for their disease. Given the availability of Ceredase, finding these “treatment naïve” patients was no easy feat: Most people with the disease were already being treated. To find enough patients who had never been treated for the disorder required an enormous, and expensive, multi-year search that has delayed access to the medicine.

Meanwhile, in 2009, there was a significant shortage of a drug called Fabrazyme, which treats another lysosomal disease: a condition called Fabry disease, which resembles Hunter syndrome and Gaucher disease. The shortage was caused by a serious manufacturing problem at Genzyme, the only company with FDA approval to market the replacement enzyme for this particular disorder. Finding itself in a pinch, the
FDA let another company distribute, free of charge, its version of the same enzyme drug, which had been approved in Europe but not yet in the United States. Patients used that drug, called Replagal, with the FDA’s permission for almost two years before its manufacturer, Shire, reached an agreement with the agency to file for formal approval.

But this spring, Shire announced that the FDA had imposed insurmountable impediments to the drug’s approval—requiring such extensive studies that the company did not believe it could afford to bring Replagal to market. The agency was asking Shire to do a new trial that, according to an official company statement, “would take at least two years and is probably not economically justifiable.” Approval of Replagal for American patients, the company continued, “would only be possible in the distant future.” It is important to note that the FDA erected these hurdles for a drug that was already being widely used, with success, by hundreds of patients, and had been approved for use in Europe for more than a decade. Predictably, Shire has responded by putting the Replagal-development program on hold; Genzyme (now part of drug maker Sanofi), the company whose manufacturing problem endangered Fabry patients, will retain its monopoly on the market for treating the disease.

These increasing regulatory obstacles have had a predictable effect. There are currently no new treatments in clinical development for Hunter syndrome. Most of the companies that previously developed drugs for such lysosomal diseases have gotten out of that market or have folded. Potential new drug developers have looked at the conditions the FDA attached to the Elaprase trial and similar development procedures, and they have determined that any future studies would take too long and cost too much. Even drug makers looking at developing “biosimilar” copies of existing drugs have so far reasoned that the process would be infeasible.

In this way, the FDA’s attitude—and the requirements the agency imposes as a result—kill incentives for new market entrants, denying patients access to new technologies and continued medical improvements. These demands also further entrench established players, and the limited competition from new market entrants means that existing drugs remain hideously expensive. Fabrazyme, for example, costs roughly $200,000 a year and faces no sustained competition.

There is room for improved treatments for all of these disorders. And it is likely that the difficulties imposed by the FDA have had a broader deterrent effect that has prevented treatments for conditions about
which doctors can currently do very little. After all, to enable continued advances in medical care, innovation needs to be constant. But the current regulatory regime is a major barrier to better therapies — and thus to better lives for many suffering Americans.

**Review and Decision**

The FDA’s cumbersome approval process has been a long time in the making, but its effects are by now clear to patients, physicians, and drug makers. This has made them increasingly evident to politicians, too. One would expect that this growing awareness would prompt lawmakers to seek some remedy, and they have — but legislative fixes will succeed only if they are rooted in a proper understanding of the problem.

For instance, two new pieces of legislation intended to expedite the review of drugs that target serious medical conditions were passed by Congress this spring. The first is the TREAT Act, introduced by North Carolina Democratic senator Kay Hagan. This bill will allow researchers to use not only demonstrations of direct effects on symptoms, but also a broader range of scientific evidence — such as improving markers of disease activity (the release of certain proteins in the blood, for instance) — to prove the safety and effectiveness of drugs being considered for early release.

A similar bill, the Advancing Breakthrough Therapies for Patients Act — crafted by Democratic senator Michael Bennet of Colorado, Utah Republican Orrin Hatch, and North Carolina Republican Richard Burr — will allow the FDA to designate a drug as a “breakthrough therapy” when it shows an unusually robust benefit in addressing an unmet medical need. The legislation will enable the FDA to take appropriate actions to expedite the development and evaluation of such drugs. These measures include providing timelier advice to the drug maker about what information and procedures the agency will require to approve the drug; making sure senior agency managers are involved in the drug’s review from the outset; and prescribing the least burdensome possible approach to the clinical trial that the FDA requires.

But even when these bills are fully implemented — thereby giving the FDA new tools to expedite drug approval — the agency’s staff will still have wide discretion in determining when to employ those tools. Ultimately, the only way to change the threshold for approval of these sorts of drugs is to change the FDA review culture itself.
To be sure, some of the mistrust that influences that culture stems from real shortcomings on the part of American physicians and the drug industry. But some of it is also an artifact of the peculiar position in which the FDA finds itself, with the same individuals simultaneously playing the roles of detective, judge, and jury when it comes to considering new drugs for approval. The FDA must demand clinical data, process this information, and then make binding decisions about when and how drugs should be used in clinical practice based on the results of its own scientific evaluations. Reviewers feel an enormous weight of responsibility; they are subject to simultaneous and countervailing pressures to both speed up approval and prevent misuse of new drugs. To a large extent, the agency’s culture of delay is the product of conflicting responsibilities.

One way to change the culture of the agency’s reviewers, therefore, is to change the way liability is distributed. FDA reviewers could maintain their tight control over the generation and evaluation of the science involved in reviewing new drugs, but pass the actual decision to another part of the agency, or to some group outside the agency altogether. Such a reconfiguration would vest in FDA reviewers the part of the process at which they excel: The reviewers generally do a rigorous job of evaluating a new drug’s benefits and risks. But how these calculated benefits get weighed against known risks is rarely clear. It is unusual for data on risks and benefits to be so straightforward that the information firmly determines whether a drug should be approved. More often, weighing this data requires judgment; it is inherently a policy call. And having to make that policy call puts undue pressure on the scientific review process, coloring how agency reviewers ask for and evaluate data.

This problem is compounded by the fact that, over time, the FDA has increasingly allowed approval decisions to be made by more junior staff. Several decades ago, office directors — essentially the second-highest tier of agency officials — typically signed approval memos. Then this task was delegated one level down, to division directors. Today, it is not uncommon to see deputy division directors, who are decidedly mid-level staff, taking on this responsibility. More junior scientists will almost invariably have less experience, and therefore less willingness to embrace uncertainty.

The FDA can start to improve and speed up the decision process by placing these judgments in the hands of a central committee that is comprised of the agency’s most senior scientists. Detaching the
approval decision from the review division in charge of collecting and evaluating scientific data, and reallocating it to the committee of senior scientists, would ensure that both responsibilities — data collection and approval — are assigned to the people best suited to take them on. Review staff would be less tempted to use the clinical-trial process to assuage their own fears of making products available to a medical marketplace filled with doctors whom they increasingly distrust. Senior managers, in turn, would have the experience and stature to exercise the policy judgment required to make careful decisions about how to weigh risks and benefits — even in the face of the uncertainties that surround any new drug. And there is no need for legislation to bring about such a change: The FDA could simply implement it on its own.

Better still, Congress should consider a different framework for how the FDA makes final policy decisions altogether. Congress might follow the model of the European Medicines Agency — the European counterpart to the FDA — which evaluates clinical-trial information and makes recommendations about the suitability of new drugs for marketing. The key difference, though, is that a body of politically appointed (and therefore politically accountable) officials, drawn from the European Commission, ultimately decides on whether a new drug should be approved. In Europe, the entity that approves drugs sits outside the agency that evaluates them.

If FDA reviewers were relieved of the political consequences of final approval decisions, they would have more confidence and freedom to innovate in how they measure risk and benefit. They could focus less attention on medical-practice decisions — an arena that is largely beyond their practical or legal purview — and focus more squarely on the science of defining risk and benefit, which is the work at which the agency’s staff is most expert.

These two potential reforms are thoroughly complementary. To the extent that it can, the FDA should begin to separate the generation and analysis of scientific data from the policy judgment of the final approval decisions. Congress, meanwhile, should consider a broader restructuring of the agency’s authority. This sort of approach — one that fundamentally re-examines and recasts the FDA’s responsibilities — would do more than current legislative proposals to speed up the FDA’s drug-approval process without undermining the agency’s ability to protect the public.
A BETTER FDA

When the final data from the pivotal study of Elaprase were at last released in July 2006—almost two years after the study had begun—the results were impressive. Patients receiving the drug were able to walk 44 meters farther than their bodies had allowed them to prior to receiving the medication. Many of the children who got only the sugar pill, meanwhile, had shown no improvement.

Science Daily relayed the experience of 16-year-old Cody Paxton, who was one of the first patients enrolled in the trial. “My breathing is better, and I’m more energetic,” the boy said; he also reported much more flexibility in his joints. He could place a hand behind his head, which he couldn’t do before receiving Elaprase. Most of the patients forced to take the placebo, however, saw their joint disease advance, making future treatment more challenging (if not impossible). Some of them would never recover the function they lost during their year on the dummy pill.

FDA reviewers are not oblivious to these human costs. But the culture in which they operate is not well suited to minimizing them. By implementing a few key structural reforms, both Congress and the FDA itself could change this counterproductive agency culture. In so doing, they would also dramatically improve the FDA’s ability to keep the American people both healthy and safe.