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White Paper

FOSTERING RESILIENCE IN THE MEDICAL MARKETPLACE:

A Plan for Reform of Pharmaceutical Regulation

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EXECUTIVE SUMMARY

What is the best way to regulate the market entry of new drugs and biologics in a manner that fosters medical innovation, yet does not make unsafe or unproven products available to doctors and patients? The U.S. Food and Drug Administration was established to make sure that medical products are safe and effective prior to broad availability. Over the years, the FDA has strayed from its mission by mandating clinical trials that require far more than evidence of safety and effectiveness; this has driven up drug development times, costs, and prices. Poor Congressional oversight has not only failed to rein in the FDA; it has also significantly contributed to the problem. We propose categories of medical evidence upon which approval decisions can be made. This would refocus the FDA on judging products by using appropriate clinical measures and on communicating to the medical marketplace the nature of the evidence supporting its safety and effectiveness decisions.

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INTRODUCTION

As the pace of change in medicine continues to accelerate, one may well ask: Is the venerable U.S. Food and Drug Administration (FDA) ready for the future? How can the FDA best deal with emerging change and innovation in medicine?

PART I: FINDING THE RIGHT POLICIES

The late political scientist Aaron Wildavsky identified two broad strategies for dealing with technological change, which he labeled *anticipation* and *resilience*. Anticipation strategies are based in risk aversion and involve centralized regulation to prevent errors. Resilience strategies are oriented toward discovery and learning, and they involve decentralized trial-and-error risk-taking.[i] The hard questions for practical policymaking in health care are when and where one or the other strategy should be followed in order to generate improvements in health. What forms of innovation and risk taking should be subject to centralized oversight, such as premarket approval of drugs and devices by the FDA? What potential activities or developments in the medical marketplace should be precluded or blocked by anticipatory regulation? How can we place daunting responsibilities on the FDA while also improving the resilience of the medical marketplace?[ii]

Balancing Anticipation and Resilience

In 1988, Wildavsky's book *Searching for Safety* suggested that in general U.S. policy had overused anticipation strategies, such as "forbidding the sale of certain medical drugs," and neglected resilience strategies, such as those manifested in "an innovative biomedical industry that creates new drugs for new diseases."[iii] We believe that in the three decades following Wildavsky's book, in pharmaceutical policy, there has been still greater emphasis placed on anticipation, on avoidance or extreme minimization of risk. Like Wildavsky, we see merit in tipping the balance back toward resilience. Many of the new developments in technology and medicine give strong reason to believe that decentralized approaches will deliver improvements in overall safety and health, with the successes helping the medical system as a whole be better equipped to mitigate the occasional failures.[iv]

The increasing policy emphasis on centralized regulation by the FDA is perhaps surprising. For over the last two decades, learning from others' experiences has become vastly easier. Results that are observed by doctors and patients, or that are obtained by experimenters anywhere, can be readily shared and accessed worldwide, even without the need for any single repository to serve as a central hub.[v] The learning benefits of centralized trials and collation of information have declined relative to those from decentralized studies, experiences, and sharing of knowledge. So one might expect that, since information is today much more readily shared and converted into useful learning, doctors and patients would be permitted to engage more freely in trial-and-error use of new safe and effective products, should they see fit.[vi]

But in many ways, the boundary has been moved in the other direction, reducing such freedoms. Mandated premarket trials of new drugs have become more complex, longer, and larger, thus delaying or simply suppressing many drugs.[vii] The FDA's standards for permitting a new drug have become more restrictive, with predicted clinical utility increasingly displacing the statutory standard of safety and effectiveness, with the same results of product delay and suppression.[viii] Furthermore, the FDA has been granted substantial new power to compel manufacturers to conduct clinical trials of drugs that have already received FDA approval and are on the market.[ix] Generally the trend is toward greater stringency, along with more resources for the FDA. Spending by the FDA's Human Drugs Program has risen sharply in recent years, while the number of new drug reviews conducted by the FDA has remained essentially flat (see Figure 1).[x]

Increased FDA spending could certainly be very sensible if the value returned is commensurate. The typical FDA review today may or may not be too costly, given the value of the assurance it provides.[xi] But what if, as many believe, decentralized experimentation is on the verge of achieving an unprecedented expansion in the number of safe and effective products—an era of individualized medicine, with better targeting of diseases and patient populations?[xii] Conventional microeconomics would predict that the FDA's marginal cost to conduct a review would increase, perhaps sharply. But what if the increase in the product pipeline was very large, perhaps to some multiple of its present size?[xiii] Given that large recent increases in funding have produced no increase in reviews conducted, it seems doubtful that the FDA could expand its capacity to deliver several times the number of such reviews it conducts today, when each review is expected to deliver prediction and assurance of ultimate clinical utility—often through large trials with long design and execution phases—rather than assurance of safety and effectiveness.

What would actually happen, though, if no change were made in expectations about what the FDA delivered, but the number of potential products started to increase dramatically? The FDA could adjust by reducing the ambition of its reviews while asserting to the public that nothing has in fact changed—a very poor outcome, as it would result in the provision of phony assurance. Another possibility, perhaps comparably poor, would be for the FDA to make alterations in the culture and rules of drug development that would block,

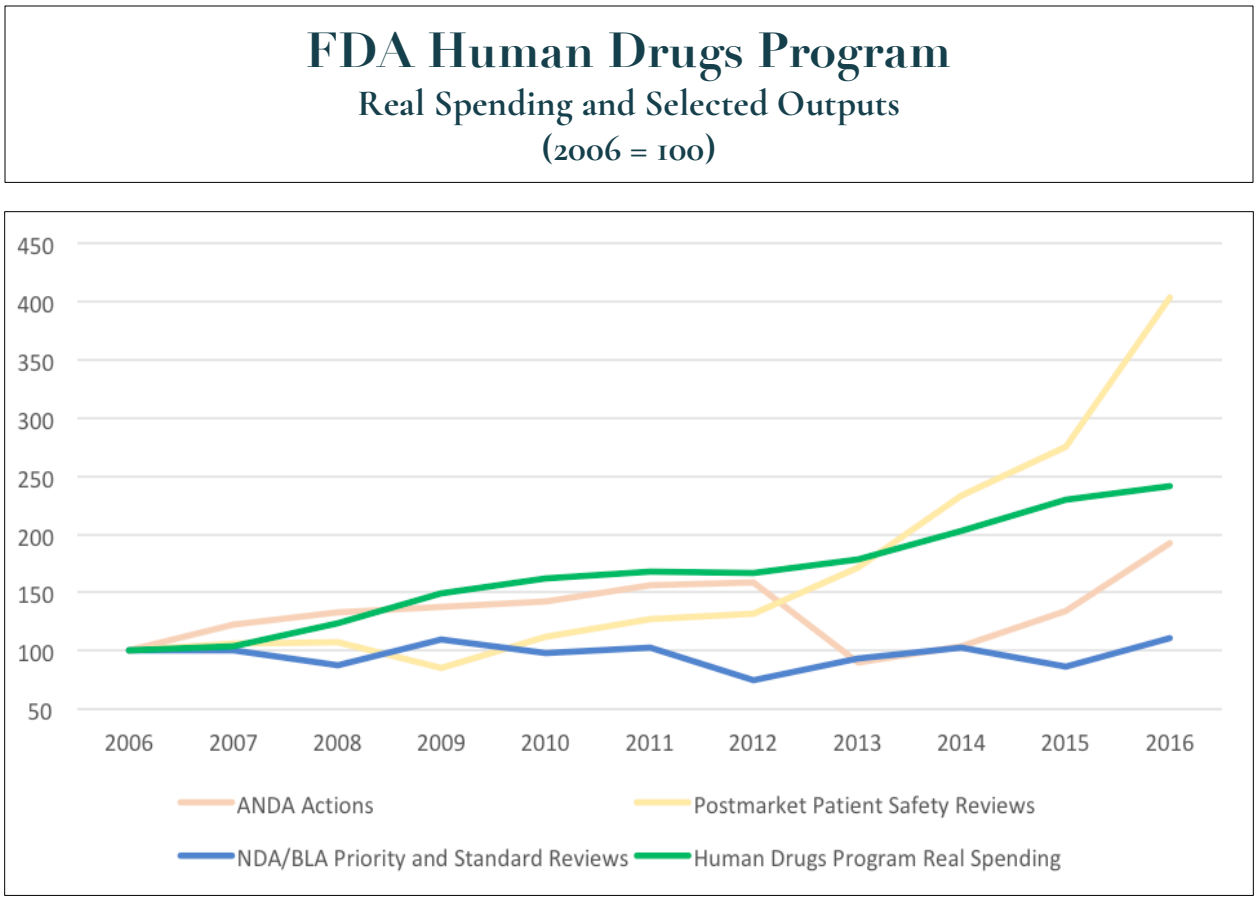

Figure 1. Source: US Department of Health and Human Services, Food and Drug Administration, *Justification of Estimates for Appropriation Committees*. (Note: Years are fiscal years. This chart is indexed relative to FY 2006 values.)

deter, or otherwise prevent products from coming up for the reviews that the FDA would not have the capacity to conduct. As Daniel Carpenter notes, the FDA "has been endowed with the ability to shape, accelerate, and even cut off the pipeline of new products in several different industrial sectors, and with the capacity to mold the scientific methods and research agendas of thousands upon thousands of scientists and physicians throughout the world."[xiv] So, for example, FDA officials could make clear, in one way or another, that they were unwilling to approve certain types of products—and thus no company would bother to bring such products forward, thereby reducing the number of reviews the FDA would be expected to conduct. The poor result would be a stifling of much technological change.

The prospect of a large increase in the number of safe and effective new drugs is, all else being equal, a reason to support overt reforms to the FDA review process. Ideal reforms would enable the FDA to produce reviews in much larger number each year while enhancing the accuracy of the FDA's communication with the medical marketplace.

We support reforms that would make it widely understood that the FDA is to conduct reviews that assure safety and effectiveness when a product is used as labeled but do *not* require evidence of purported clinical utility. Clinical utility is an elusive standard—it is tantamount to proving that there are, in some overall and ultimate sense, benefits to patient health from a product. Generally, even the best science cannot produce conclusive evidence on such a question, as attested by the many conflicting studies of the health effects of aspirin, for example. Aspirin is a safe and effective product, when used in accordance with its labeling—it generally delivers the promised effect to alleviate pain—but scientists continue even today to investigate whether taking aspirin is ultimately "good" when gauging different health risks, for different types of patients, over the long run, and so forth. Certainly, we would like to know the answers to these questions, and those studies are valuable and consequential for medical practice, yet it is obvious that aspirin should not be banned now because of such ongoing debates. If we do not have the answers on ultimate patient outcomes from taking aspirin—an intensely studied and widely consumed product—there may be little chance of correctly identifying ultimate health outcomes from any given new drug. But, as with aspirin, a well-designed study can tell us about the safety and effectiveness of a new drug in delivering a certain promised effect. The standard that would allow physicians to prescribe an aspirin-like drug—"mere" safety and effectiveness when used as labeled—should be the standard we apply in determining whether physicians will be allowed to prescribe a new drug. Physicians, patients, researchers, payers, and others in the medical marketplace would then make judgments of the clinical utility of the therapies after approval.[xv]

A change in U.S. policy, such that new drugs are approved on the basis of safety and effectiveness (not on the basis of purported clinical outcomes that are deemed important by the FDA), would be a very meaningful shift toward the resilience strategy in medical innovation. Effectiveness should be judged by whether the drug, indeed, does what the drug developer says it does—that it is not snake oil. Of course, the drug developer is induced to undertake the tremendously time-consuming and costly development process in order to provide drugs that satisfy the needs of the medical marketplace. The shift toward resilience would be extraordinarily valuable in providing clarity with regard to the division of labor in the production of medical knowledge. Today, it is likely a common belief that premarket studies are able to conclusively demonstrate whether a drug has clinical utility, with the result that clinical utility is insufficiently studied in the postmarket setting and instead is mistakenly presumed to exist. But overt reform would make clear that the FDA assures safety and effectiveness, while the ongoing responsibility to tackle questions of clinical utility rests primarily outside the FDA. To truly obtain the gains in health available from greater emphasis on the resilience strategy, then, we would be (knowingly) relying on researchers, doctors, payers, and reputational mechanisms in the medical marketplace—mechanisms that are

today greatly enhanced by the fortunate advances in information technology—rather than presuming (or imagining or hoping) that one small government agency has somehow already done all the work.[xvi] The medical marketplace has always performed myriad operations to assure drug quality, and of course, the system has and will continue to rely on good work by the FDA.[xvii]

In this paper we suggest that the FDA establish categories or orders of approval according to the nature of the evidence used to support effectiveness claims, a system that we believe will add substantial value atop the informational functions that premarket approval already serves. This will relieve the FDA from dictating clinical endpoints to drug developers, yet leverage the FDA's significant expertise in communicating product knowledge to physicians and patients. It will also increase efficiency in the drug development process by enabling drug manufacturers to match the size, scope, duration, and goals of preapproval clinical studies with the claims being sought, in response to the demands of the medical marketplace—efficiency in addressing medical needs with new products, responding to the activities of competitors, and satisfying payer requirements

Such reforms will assure that the FDA is restored to its proper place at the top of the medical marketplace funnel, as described in our earlier paper.[xviii] The Federal Food, Drug, and Cosmetic (FD&C) Act introduced a balance of anticipation and resilience strategies for dealing with technological change in medicine. In the FD&C Act, Congress has outlined the proper role of the FDA: permitting safe and effective products onto the market, with the medical marketplace determining how best to use them. Congress implemented preapproval requirements (anticipation) and postapproval vigilance (an institution that underpins resilience) as complementary methods that the FDA would use to issue and withdraw *permission*. After approval, it is then supposed to be the work of the medical marketplace to make determinations with regard to *adoption* of permitted products, both for uses according to the labeled claim and for off-label uses. Learning and selection processes, working alongside FDA-led vigilance for emerging safety concerns, narrow the

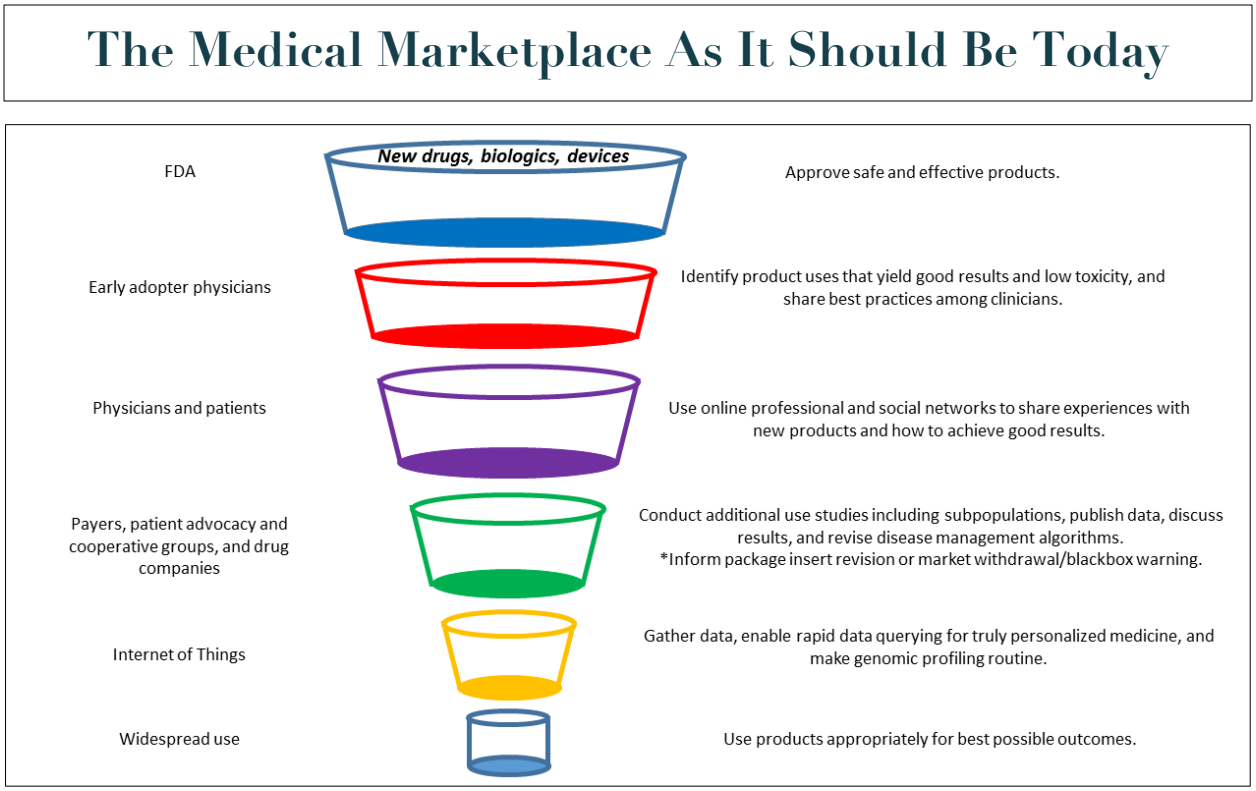

Figure 2. The Medical Marketplace As It Should Be Today. *Source:* Gulfo, Briggeman, and Roberts, "The Proper Role of the FDA," 21.

funnel by identifying optimal uses of available safe and effective products (see Figure 2).

The reforms are needed because over the past two decades the FDA has drifted away from its mandate for judging safety and effectiveness, shifting the balance toward preapproval requirements and away from postapproval vigilance. Why has that unfortunate shift at the FDA happened? How has it been allowed to occur, and what can we do to reverse it? How can policy be changed, on the ground, in terms of practical political and governmental action? We now turn our attention to what Congress can do.

PART II: FIDELITY TO THE LETTER (AND SPIRIT) OF THE LAW

How can we place more emphasis on strategies of resilience in pharmaceutical development and less emphasis on centralized anticipatory regulation?

Congress certainly expends great effort passing laws that have the goal of enhancing medical innovation—for example, the reauthorizations of the Prescription Drug User Fee Act (PDUFA) and Medical Device User Fee Amendments (MDUFA). But we believe Congress has leaned too much on new *legislation* to accomplish its goals. So much legislation has been passed by previous Congresses that today few in Congress or at the FDA know the existing law.[xix] The pressing need now is to ensure that the letter, intent, and spirit of the laws that have passed are not lost in rulemaking or in the drafting and implementation of guidance documents.

Unfair "Fire Alarm" Oversight Can Create a Vicious Cycle

Unfortunately, of the oversight that Congress has conducted in the past, much has been of a pernicious form. Regular, fair "police patrol" oversight by Congress would hold the FDA accountable for failure to dutifully carry out the law. But often Congress has conducted "fire alarm" oversight—investigating in reaction to a perceived crisis—and unfairly cast blame upon the FDA for outcomes in the medical marketplace. "Fire alarm" oversight has often had severe and lasting unintended consequences.

When faced with a Congress that seeks to blame the FDA when toxicities emerge from the use of approved products, the FDA has reacted in the following manner:

1. The FDA moves its regulatory emphasis further toward preapproval requirements, as opposed to postmarket controls—exacerbating an imbalance that Shannon Gibson and Trudo Lemmens term "premarket syndrome"[xx]—thereby adopting a "protect health" posture, at the expense of its "promote health" mandate as defined in the law.

2. The FDA restates approval standards, shifting from safety and effectiveness—based on substantial evidence that the drug will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling submitted for review by sponsors—toward purported clinical utility and clinical benefit (as defined by the FDA, not by sponsors), as well as to survival and disease outcomes. And searching prior to market entry for elusive evidence of clinical utility generally means larger and longer trials than those needed to demonstrate safety and effectiveness.

3. The FDA seeks to limit the populations that new drugs are approved to treat, hence, the unprecedented rise in orphan drug designations—340 of them in fiscal year 2016—and approvals for niche specialty claims in recent times.[xxi]

These three actions reduce the likelihood that the FDA will be ridiculed in the future for toxicities that may occur with the use of approved drugs. But they also severely hinder the development of

new products that may be of great help to patients.

Instances of "fire alarm" oversight include the high-profile hearings on drugs such as Vioxx, Rezulin, and Avandia. Recently, calls have been made for congressional hearings on surgical meshes, intrauterine devices for birth control, and endoscopic equipment that spread antibiotic-resistant infection. In all of these, the FDA is basically accused of inappropriately approving products that are unsafe; of course, the issues are not so cut and dried.

The case of Avandia is particularly disconcerting, as it suggests that even when the FDA does the right thing—for example, approving an excellent drug that helps millions of patients—it can be castigated and publicly humiliated. In 2007, a *New England Journal of Medicine* publication of a meta-analysis of 42 small clinical trials revealed an increased likelihood of significant cardiovascular toxicity in patients taking the drug, so the FDA restricted the drug's use in response to pointed criticism from Congress. Here is what the FDA had to endure at a House subcommittee hearing on the matter:

> *This report poses several troubling questions for this subcommittee. Most obviously, if Avandia is unsafe, how did it ever get on the market in the first place? For that matter, why is it still on the market, right now? And what does the case of Avandia tell us about the FDA's current ability to conduct its drug safety responsibilities?*[xxii]

Subsequently, in 2013, the FDA removed the restrictions from Avandia's label when it was shown not to cause increased cardiovascular problems, following a re-analysis of a very large prospective study that showed the earlier meta-analysis to be flawed. Then, in December 2015, the FDA said "continued monitoring" of Avandia, Avandamet, and Avandaryl had turned up "no new pertinent safety information" about the drugs,[xxiii] so the agency lifted the final layer of safety measures that it had imposed. But sales of the drug had been crushed; as reported by FiercePharma, "The safety questions drove Avandia revenues down from a peak of $3 billion before the controversy to $183 million in 2011, just before generics hit the market."[xxiv] And the broader damage was done: The initial Avandia controversy was central to a "watershed year" in the movement toward requiring larger and larger clinical trials and disease outcome endpoints for products that are intended for large-population chronic diseases like diabetes.[xxv]

Congress's failure to conduct the good "police patrol" form of oversight compounds the problem of the FDA's deviation from the law in reaction to "fire alarm" oversight. After the "fire" is smothered, Congress does not "police" the FDA to bring its practices back in line with the law; it does not re-instruct the FDA that its mission is to promote health as defined in the statute; and it does not redirect the FDA to uphold safety and effectiveness as the standard for approval. Congress has actually reinforced the embattled regulator's fear-driven preference for drugs for small-population diseases by passing laws like the Food and Drug Administration Safety and Innovation Act (FDASIA) (with its breakthrough therapy designation) and the 21st Century Cures Act (including priority review for breakthrough devices and many other provisions), which largely focus on orphan conditions, those affecting fewer than 200,000 patients per year.

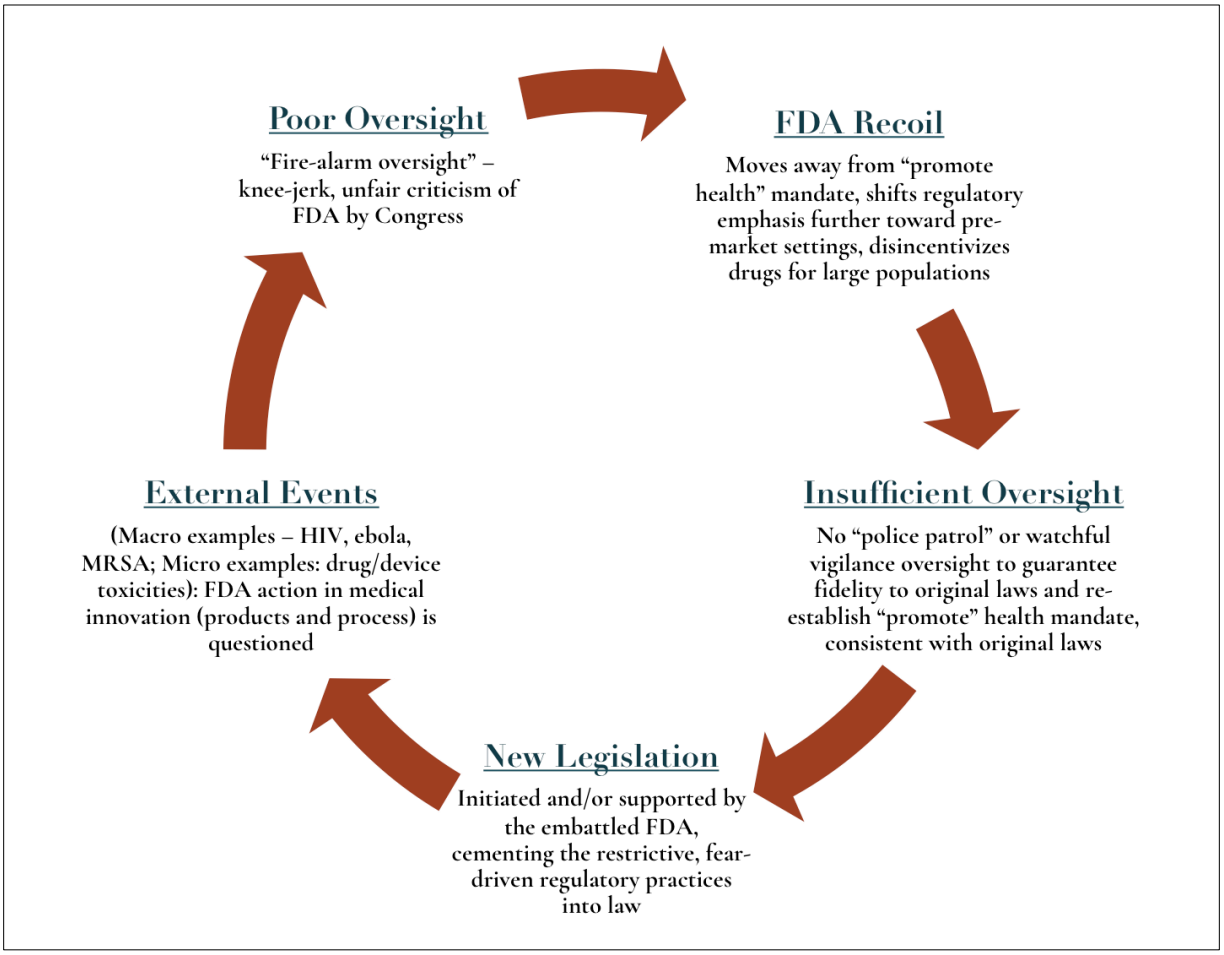

Figure 3: The Vicious Cycle.

Figure 3 offers a visual representation of a vicious cycle that can result when only the "fire alarm" form of oversight is conducted:

1. External events, such as the emergence of public health crises (e.g., Ebola, HIV, methicillin-resistant staphylococcal infections) or adverse events apparently linked to approved products (e.g., Avandia) call into question the adequacy of the FDA's approval policies.

2. "Fire alarm" oversight is initiated, publicly humiliating the FDA when FDA-approved products are associated with the undesired events.

3. The embattled FDA recoils, including a relative shift toward focus on preapproval requirements (away from postapproval vigilance) and a migration of the approval standard from effectiveness to clinical utility (see Figure 4).

4. After the crisis passes, there is a lack of good "police patrol" oversight that would force the FDA to comport itself in accordance with the law after the FDA had—understandably, but ultimately out of fear—moved away from the law by implementing overly restrictive practices.

5. Unnecessary and contradictory legislation, initiated or supported by the embattled FDA, is passed by Congress, muddling the law and thus effectively cementing the decisions that the FDA had made in reaction to the unfair "fire alarm" oversight.

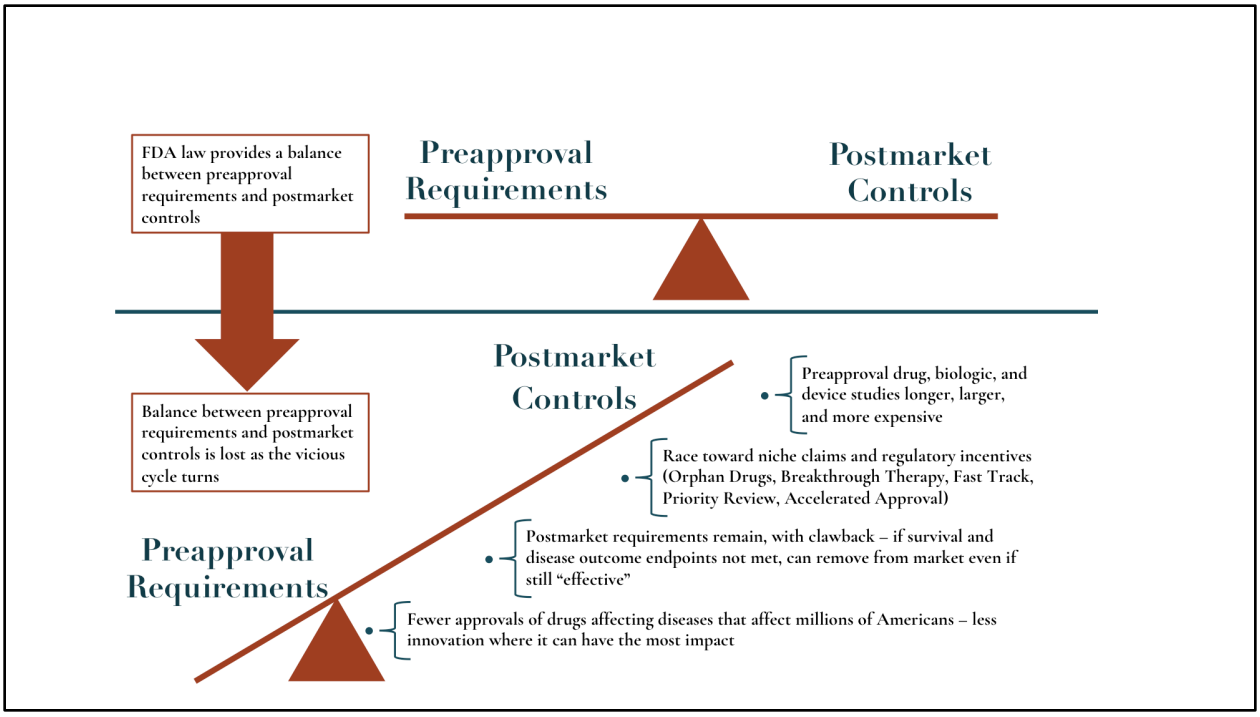

Figure 4: Preapproval Requirements and Postmarket Controls

Figure 4 illustrates how the balance of preapproval requirements and postapproval controls shifts with each turn of the vicious cycle. It also illustrates how the nature of the preapproval requirements and postapproval controls are modulated.

How can Congress avoid pulling the "fire alarm" in the future? While self-binding legislation may not be possible, a symbolic resolution may go some ways toward creating a new and important norm: that members of Congress should refrain from using hearings as a venue to publicly embarrass and humiliate the FDA when it happens that an approved product is shown to have undesirable effects and toxicities when used in the real world. Such actions set off the vicious cycle (Figure 3) that stifles medical innovation. Those actions also set an expectation in the eyes of the public for the FDA to be perfect when it comes to the review and approval of new products.

But we should not be conditioned to expect perfection from FDA; rather, we should be assured that proper mechanisms are in place to appropriately judge the safety and effectiveness of new products and to track them and rapidly report any issues that might emerge after approval. The FDA should then act appropriately, either with revised labeling or other actions, including removal from the market in extreme instances. And Congress would do well to reinforce for the public that the FDA, while exceedingly important, is only one hub of the medical ecosystem.[xxvi] Physicians, medical societies, hospitals, cooperative research groups, drug companies, and clinical researchers have an important responsibility to disseminate information quickly and to educate medical professionals and the public. Laying blame at the door of the FDA is neither accurate nor conducive to fostering medical innovation.

Bipartisan agreement on this last point has been achieved in recent years. At a Senate hearing in 2016, Ron Johnson, chairman of the Senate Committee on Homeland Security, stated that "part of the problem has been things like congressional hearings. . . . When members of Congress beat up on the FDA . . . they become even more risk-averse." Minority leader Tom Carper concurred, saying, "I call those 'gotcha panels.'"[xxvii] Clearly, this form of oversight does not help to ensure that the FDA follows the letter and spirit of the laws, which are designed to promote innovation; rather, it does the exact opposite.

PART III: PROPOSALS FOR INSTITUTIONAL REFORM AT THE FDA

For the reasons explained above, proper congressional oversight of the FDA going forward cannot make up for the problems that have been caused by the lack of good oversight over decades—additional changes should be considered in order to essentially reposition the FDA on its foundations.

Promoting Health Is the FDA's Principal Function with Respect to Drugs and Devices

The law defines the FDA's mission: "To promote health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion." Of course, protecting health is part of promoting health; however, the FDA has elevated "protecting" health to its main mission. Promoting and protecting health are two different postures—the latter looks to preserve that which currently exists, while the former implies optimism and belief in the advancement of scientific discoveries as a means of improving the health of Americans.

Implicit in promoting health is an understanding that new products occasionally may not be found to be as desirable as we would like them to be. The law as written embraces medical innovation by assuming that new drugs that undergo the drug development gauntlet would be approved *unless* the drugs (or applications) had certain deficiencies.[xxviii] The law also provides for a balance between preapproval hurdles and postapproval controls, and it makes clear that approval should not be denied in cases where questions about a drug or device could be addressed in the postapproval setting via postmarket controls (studies, vigilance, and surveillance). But these "promoting health" attitudes and inclinations are not embodied in many FDA regulations and guidance documents, nor are they found in some sections of recent reauthorization legislation.

Affirm Safety and Effectiveness as the Only Requisite Standards for Approval of New Products, and, for Devices, Affirm the Reasonable Assurance Standard and the Least Burdensome Approach

As often happens when a bureau has been allowed to operate outside its original mandate for an extended period of time, putting the genie back in the bottle, so to speak, is not possible. Through several turns of the vicious cycle discussed above, the FDA has strayed from using safety and effectiveness as the sole conditions of approval, and it has shifted the emphasis from a balance of preapproval requirements and postapproval vigilance, such that preapproval requirements now dominate the regulatory paradigm.

As we described in our paper "The Proper Role of the FDA for the 21st Century," those two developments have put the FDA in the position of dictating to the medical marketplace which products are most beneficial and for whom, as opposed to its rightful position as gatekeeper, permitting safe and effective products onto the market for the medical ecosystem to determine ultimate clinical utility for individual patients. This is untenable for many reasons, including not only the exorbitant development costs and time to conduct preapproval clinical studies to satisfy the FDA's vision of clinical utility, but also our general inability in such studies to control for the many factors that determine ultimate disease outcomes.[xxix]

It should be affirmed that the FDA is to evaluate effectiveness in accordance with the labeling proposed by the sponsor and that the FDA is not to require demonstration of clinical utility for approval. The FDA can and should limit the claims that the sponsor can make to only those claims based on the data: If there are no clinical utility data in the application, then clinical benefit

should not be claimed. For example, if a drug that lowers LDL cholesterol was not studied to determine whether its use reduces myocardial infarctions, then the claim would be limited to cholesterol reduction and could not include statements about lowering risk of myocardial infarction.

A drug's approved label should contain the measures used to determine effectiveness, and the approved claims should be limited to the specific findings. There should be an explicit list of acceptable measures of effectiveness that can support approval, including pharmacodynamics effects on disease parameters, clinical signs and symptoms, biomarkers, surrogate endpoints, patient-reported data, comparative effectiveness, clinical outcomes, and survival. And there should be a strong caveat that those last three measures—comparative effectiveness, clinical outcomes, and survival—are not *necessary* to demonstrate effectiveness. The FDA's insistence on such measures has often needlessly delayed or suppressed useful drugs, rendered drugs more expensive by dampening market competition, and created unintended consequences in drug development patterns. An apparent example is the relative intensity of research into treatments for late- and early-stage cancer. Simply because of the nature of terminal disease, a study of a drug's effect on survival in late-stage cancer will be briefer, and will more readily yield convincing results, than a study of a drug's effect on survival in early-stage cancer. Thus, regulator insistence on demonstrated survival improvements likely causes impact-oriented researchers to emphasize late-stage cancer treatments, relative to early-stage treatments, more than they otherwise would have. The economists Eric Budish, Benjamin Roin, and Heidi Williams accordingly have found substantial evidence that approval of drugs for cancer and heart disease on the basis of valid surrogate endpoints may yield large gains in patient health.[xxx]

The reform here proposed should serve to foster discovery of beneficial drug combinations. Drug combinations, meaning the administration of two or more drugs together, can be necessary to obtain a large beneficial effect for a patient, which is to say that the independent use of any single drug in the combination would deliver little or no clinical utility. Drug combinations are vital today in the treatment of cancer, cardiovascular disease, infectious diseases, and Alzheimer's disease.[xxxi] Using drugs in combination poses risks, of course—the possibility of an undesirable "interaction" between drugs is well-known. It must be emphasized that our proposed reforms mean to allow onto the market only those drugs that can safely deliver a certain biological effect, such as improvement in a biomarker. A given combination of two or more drugs that are each known to safely deliver a biomarker improvement might, perhaps, have an unfortunate interaction—but so might a given combination of two or more drugs that are each known to safely deliver a clinical outcome.

Making a greater number of possible combinations of safe drugs available to the medical marketplace does mean more *possible* harmful combinations, but also more *possible* very successful combinations—and the prospect of learning in the medical marketplace should mean there will be a strong tendency for harmful combinations to be dropped, reported, and thereafter avoided, while very successful combinations will tend to be continued, tried in additional settings, studied, and then brought into widespread use. As our understanding of the multifactorial nature of complex diseases grows, having drugs with proven biological effects available on the market will allow academic and corporate researchers to expeditiously evaluate rational combinations that could not otherwise be studied. This would also further enable and accelerate personalized therapy.

Affirm that the FDA Can Establish Orders or Categories of Approval

The FDA should be permitted to establish categories of approval according to the nature of the evidence used to support effectiveness, and if sponsors desire additional, higher-order categories (for example, survival and disease outcomes), they can submit supplemental approval applications. Such a system might provide for three or

four categories of approval, as in the following example using four categories.

Category 1: Biomarker

> *improvement in a biomarker known to be elevated or decreased in patients with specific diseases—for example, fasting blood glucose, hemoglobin A1c, carcinoembryonic antigen (CEA), CD4/CD8 ratio, prostate specific antigen (PSA), blood clotting (INR), LDL cholesterol, HDL cholesterol, etc.*

Category 2: Clinical Signs and Symptoms

> *reduction in pain; improvement in activities of daily living; tumor response (size, local control, improved progression-free interval); improvement in forced expiratory volume; improved walking distance; improved bone mineral density; improved treadmill performance and EKG findings (atrial fibrillation, premature ventricular contractions); patient-reported outcomes; etc.*

Category 3: Disease Modulation

> *reduction in flares of diarrhea, arthritis, or headache; reduction in suicidal ideation; fewer heart failure readmissions; reduction in joint space narrowing; reduction in use of other medications (steroids); reduction in development of deep vein thrombosis or pulmonary embolism; reduction in unstable angina; etc.*

Category 4: Clinical Outcomes

> *improvement in survival; reduction in major cardiac events (myocardial infarction, heart failure, rehospitalization); etc.*

This example of a four-category system for drugs is described in greater detail in the Appendix, along with similar examples for diagnostics and devices.

A somewhat similar system is already in place in the accelerated approval pathway implemented under FDASIA.[xxxii] As an illustration, consider the claims language for two cancer drugs, Ibrance[xxxiii] and Keytruda,[xxxiv] where progression-free interval and response rate, respectively, served as the bases of accelerated approval, while improvement in survival is required by FDA for the drugs to be granted "full" approval. But our proposal differs from the accelerated approval pathway in two fundamental ways. First, we propose that manufacturers have the option—as opposed to being required—to conduct additional studies to obtain a higher-order effectiveness claim. This decision would be driven by market forces, including consumer (payer, doctor, and patient) demands and competition. The FDA could not demand that a company apply for a particular (higher) order of effectiveness. Second, these approvals would not be conditional, meaning, for example, unlike the accelerated approval pathway, the FDA could not revoke an approval that is based on biomarkers (Category 1 in our example) if a subsequent study did not show a survival advantage (Category 4). But approval could be revoked for safety issues or if studies subsequent to premarket approval did not show a favorable trend in the endpoint used to obtain the drug's current approval.

The FDA's implementation of orders of approval that are based on the nature of the medical evidence used to substantiate effectiveness would provide clear and unambiguous regulatory pathways to approval without undermining the FDA's authority to adjudicate safety and effectiveness.[xxxv] It is also straightforward: Language in the claim itself would clearly communicate to physicians the most important information about the drug and the effect that physicians can expect from its use. To that end, our system should provide improved transparency and clarity in the approval process and more comprehensible communication to physicians and patients.

With enforcement of the effectiveness standard (categories of approval based on the nature of the evidence used to validate activity) and with the FDA meeting its review time frames, programs such as breakthrough therapy designation, accelerated approval, fast track, and priority review would no longer be needed and could be dropped.[xxxvi] Designations for orphan drug and qualified infectious disease product should remain.

Postapproval Studies Should Be Required Only in Well-Defined Situations

Requiring postapproval observational studies to amass additional safety data is appropriate. However, postapproval clinical studies to determine, for example, whether a new drug increases the rate of major adverse cardiovascular events, should be required only subsequent to an advisory committee recommendation or if a hazard signal was observed in preapproval clinical trials or postapproval observational studies. Importantly, the FDA's determination of safety should be made relative to the conditions of use specified by the sponsor, per the FD&C Act—"safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling"—not in anticipation of potential uses or abuses of the product outside of the claim sought in the approval application.

And again, postapproval studies performed to generate evidence for higher-order effectiveness claims should not result in market withdrawal if it is merely the case that higher-order effectiveness objectives are not met. But package inserts should be updated regularly with new study results, including any studies that, for instance, fail to find that a drug's effect on a biomarker correlates with clinical outcomes. This is in contrast to the current regulations, which allow for rescinding product approval if drugs approved on the basis of surrogate endpoints are not shown to have improved disease outcomes and survival in postapproval studies, as occurred with Avastin for the treatment of breast cancer.[xxxvii]

Clarify Which Decisions Are the Domain of the FDA (Public Health) and Which Are the Domain of Physicians, Patients, and Others in the Medical Marketplace

Personalized medicine should be fostered. The FDA is responsible for safety and effectiveness, while clinical utility and clinical benefit often cannot be easily assessed or analyzed in studies of the "average patient" because they can vary greatly from patient to patient. If sponsors propose claims that communicate clinical utility and clinical benefit, then they must present data to the FDA that supports these claims in a meaningful percentage of patients, even if the exact profile of responding patients cannot be defined for labeling purposes, either demographically or genetically. To further foster personalized medicine, data from clinical trials used in regulatory filings to support approved claims should be made publicly available so that knowledge of the effects of the drugs on patients with certain demographic and genetic profiles can be developed and accessed. This will aid physicians as they decide how to prescribe and use drugs with individual patients in real-world situations.[xxxviii]

These reforms will reverse the erosion of the original intent of the law, reaffirming that the regulatory standard of effectiveness is to mean biological activity, with clinical utility to be defined and refined within the medical ecosystem. The FDA's premarket reviews will recognize multiple measures of biological activity and communicate clearly about them, which will allow more expeditious entrance into the medical armamentarium by new drugs that demonstrate safety and effectiveness. Postapproval studies performed by manufacturers, payers, hospital consortia, and medical societies will determine which drugs provide clinical benefit for patients. In turn, research and development priorities will flow more from demand and developments in the broad medical ecosystem, and they will be less a function of variation in the FDA's stances.

CONCLUSION

We have observed that the FDA has not only moved away from its proper role in the medical marketplace, but has also been permitted to redefine its Congressional mandate. The FDA is supposed to expeditiously judge whether a new drug

can be labeled for safe use and whether substantial evidence exists that the drug will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling submitted for review by sponsors. However, the FDA frequently has adopted the position that purported clinical utility and clinical benefit (as defined by the FDA, not by sponsors), as well as survival and disease outcomes, are required for approval. This has greatly handicapped medical innovation and has redirected drug development away from diseases that affect millions of Americans and toward niche diseases. It has also added to the long lead time and enormous cost of developing new drugs, which, in turn, drive drug prices upward.

But the FDA is not at all solely to blame. Drug companies blindly paying higher and higher user fees without effectively articulating the need for reform to the American public are getting what they deserve. A great deal of culpability lies with Congress for adding to the morass of legislation, often cementing the FDA's deviations, and for not exercising proper oversight. The net result is that the FDA has imposed more and more preapproval standards, seeking to anticipate and even define medical practice, while missing opportunities to implement effective and collaborative postmarket monitoring, which would foster resilience in the medical ecosystem.

A vicious cycle of "fire alarm" oversight (which begins when toxicities emerge with marketed products), a lack of "police patrol" oversight (when the FDA strays from its congressional mandate), and overcompensating legislation (for example, with every PDUFA and MDUFA reauthorization) have gotten us to this point. More effective and regular oversight of FDA by Congress is desirable. Unfortunately, current practices are so far from the spirit of the law that remedial legislation is also necessary to put the train back on its tracks.

The most important element of needed reforms is to provide for tiered categories of approval of products that can be labeled for safe use according to the evidence used to validate their clinical activity. A four-part effectiveness determination paradigm would cover (1) biomarkers, (2) clinical signs and symptoms, (3) disease modification, and (4) long-term outcomes. This would put the FDA in the proper position of adjudicating safety and effectiveness, and it would help the FDA to clearly communicate to the medical marketplace its rationale for approval and the clinical effects that doctors and patients can expect when using new drugs.

APPENDIX A: FOUR-CATEGORY SAFETY AND EFFECTIVENESS PARADIGMS

A.1. Drugs and Biologics

Proposed safety and effectiveness paradigm based on type of evidence provided			
Safety: determination of safety is to be made relative to the conditions of use specified by the sponsor, per the FD&C Act—"safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling"—not in anticipation of potential uses or abuses of the product outside the claim sought in the approval application. Special emphasis is placed on the likelihood of use causing death, debilitation, or severe harm and on ways to mitigate these risks.			
Effectiveness: categories consistent with the nature of the endpoints used to demonstrate substantial evidence of effectiveness. Labeling will be color coded to facilitate communications to physicians, patients, and other groups.			
Category 1: Biomarkers	**Category 2: Clinical Signs and Symptoms**	**Category 3: Disease Modulation / Modification**	**Category 4: Clinical Outcomes and Survival**
Improvement in a biomarker known to be elevated or decreased in patients with specific diseases—for example, fasting blood glucose, hemoglobin A1c, carcinoembryonic antigen (CEA), CD_4/CD_8 ratio, prostate specific antigen (PSA), blood clotting (INR), LDL cholesterol, HDL cholesterol, etc.)	Reduction in pain; improvement in activities of daily living; tumor response (size, local control, improved progression-free interval); improvement in forced expiratory volume; improved walking distance; improved bone mineral density; improved treadmill performance and EKG findings (atrial fibrillation, premature ventricular contractions); patient-reported outcomes; etc.	Reduction in flares of diarrhea, arthritis, or headache; reduction in suicidal ideation; fewer heart failure readmissions; reduction in joint space narrowing; reduction in use of other medications (steroids); reduction in development of deep vein thrombosis or pulmonary embolism; reduction in unstable angina; etc.	Improvement in survival; reduction on major cardiac events (myocardial infarction, heart failure, rehospitalization); etc.

A.2. Diagnostics

Proposed safety and effectiveness paradigm based on type of evidence provided			
Safety: determination of safety is to be made relative to the conditions of use specified by the sponsor, per the FD&C Act—"safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling"—not in anticipation of potential uses or abuses of the product outside the claim sought in the approval application. Special emphasis is placed on the likelihood of use causing death, debilitation, or severe harm and on ways to mitigate these risks.			
Effectiveness: categories consistent with the nature of the data used to demonstrate substantial evidence of effectiveness. Labeling will be color coded to facilitate communications to physicians, patients, and other groups.			
Category 1: **Associated with disease or current state of disease in patients with an established diagnosis when used alone or when considered with other diagnostic tests and clinical information**	**Category 2:** **Predicts safety and effectiveness in patients receiving drug/biologic therapy**	**Category 3:** **Predicts for disease presence or progression**	**Category 4:** **Information provided by the test induces interventions that favorably alter the natural history of the disease**
Examples: 1. Measurement above a threshold is associated with disease recurrence. 2. Rising level is associated with progression of disease.	Examples: 1. Companion diagnostics. 2. Test correlates with drug/biologic effect, taken during drug therapy to determine whether: a. continued treatment is likely to be safe; or b. clinical response is likely (clinical signs and symptoms, disease modulation, clinical outcomes and survival).	Examples: 1. Screening test that enables diagnosis earlier than currently available methods. 2. Test in patients with established diagnosis identifies those at higher risk for progression and other poor outcomes (clinical measures: disease burden or severity, survival, progression, or quality of life, etc.).	Examples: 1. Screening test leads to initiation of therapy (surgery, drug, device) that results in improved survival or quality of life. 2. Test in patients at high risk or with established diagnosis leads to initiation of therapy (surgery, drug, device) that results in improved survival or quality of life.

A.3. Devices

Proposed safety and effectiveness paradigm based on type of evidence provided			
Safety: determination of safety is to be made relative to the conditions of use specified by the sponsor, per the FD&C Act—"safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling"—not in anticipation of potential uses or abuses of the product outside the claim sought in the approval application. Special emphasis is placed on the likelihood of use causing death, debilitation, or severe harm and on ways to mitigate these risks.			
Effectiveness: categories consistent with the nature of the data used to demonstrate substantial evidence of effectiveness. Labeling will be color coded to facilitate communications to physicians, patients, and other groups.			
Physical Action		**Clinical Sequelae**	
Category 1: Tools - Used in conjunction with diagnostic or therapeutic intervention (surgery or drug delivery)	**Category 2: Used to diagnose disease, to provide treatment, or to repair or replace damaged or nonfunctional or dysfunctioning tissues**	**Category 3: Clinical Improvement**	**Category 4: Improved Clinical Outcomes**
Example: 1. Used to help conduct or facilitate diagnostic or therapeutic procedures.	Examples: 1. Diagnostic equipment. 2. Eradicate, ablate, or destroy tissue. 3. Enhance, augment, or substitute functioning of tissues or organs.	Examples: 1. Improve or stabilize clinical signs and symptoms of disease. 2. Reduce complications from surgery or drug therapy. 3. Disease modulation or modification.	Examples: 1. Disease progression; progression-free survival. 2. Reduce major cardiovascular events (MACE). 3. Survival.

[i] Aaron Wildavsky, *Searching for Safety* (New Brunswick, NJ: Transaction Publishers, 1988), 1–14.
[ii] We use the term *medical marketplace* simply to invoke the idea that there is a broad world of medicine, of physicians, patients, researchers, payers, government agencies, business firms, universities, nonprofit organizations, and so forth, in addition to the (comparatively small) FDA. By this term we certainly do *not* mean only markets or only private entities.
[iii] Wildavsky, *Searching for Safety*, 77.
[iv] Joseph V. Gulfo, Jason Briggeman, and Ethan C. Roberts, "The Proper Role of the FDA for the 21st Century" (Mercatus Research, Mercatus Center at George Mason University, Arlington, Va., 2016).
[v] In the past, even those who questioned the appropriateness of the FDA's judgments would have acknowledged that the FDA, through its own file cabinets, inevitably had more access to information about drugs than did anyone else. Today, whatever information that can be housed in a file cabinet could in principle be put on a web server and made available to anyone.
[vi] Wildavsky, writing in 1988 about innovation in pharmaceuticals, already found "good reason to believe that the bulk of benefits have come not only from the original discovery, however brilliant, but from innumerable varieties produced by a sort of rough-and-ready empiricism, where incremental changes are tried out to see if they would suit a particular class of potential users." Wildavsky, *Searching for Safety*, 33.
[vii] A recent study of nearly 10,000 clinical trial protocols shows that their complexity increased considerably between 2001–2005 and 2011–2015 (Kenneth A. Getz and Rafael A. Campo, "Trends in Clinical Trial Design Complexity," *Nature Reviews Drug Discovery* 16 (May 2017): 307). An annual benchmarking study by KMR Group shows substantial general increases in trial duration between 2006–2008 and 2013–2015 (Linda Martin, "Clinical Trial Cycle Times Continue to Increase Despite Industry Efforts," *Nature Reviews Drug Discovery* 16 (March 2017): 157). A study of data from ClinicalTrials.gov does show a small decline in the scale of trials between 2004–2007 and 2007–2010 (Robert M. Califf et al., "Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007–2010," *Journal of the American Medical Association* 307 (2012): 1841). In trials of cardiovascular drugs, there is a longstanding trend toward greater complexity (Elliott M. Antman and Robert A. Harrington, "Transforming Clinical Trials in Cardiovascular Disease," *Journal of the American Medical Association* 308 (2012): 1743–44; Eric J. Topol et al., "Perspectives on Large-Scale Cardiovascular Clinical Trials for the New Millennium," *Circulation* 95 (1997): 1072–82). For a concrete example, consider the clinical trial programs that resulted in the approvals of Glucophage (metformin), the most widely used agent in the treatment of type II diabetes, and Victoza (liraglutide) in 1995 and 2010, respectively. Four randomized studies of metformin (two of 29 weeks' duration, one of 24 weeks, and one of 16 weeks) included 1,023 patients. Five randomized studies of liraglutide (one of 52 weeks' duration, three of 26 weeks, and one of 24 weeks) included 3,992 patients. The FDA also required large, multiyear follow-up studies of liraglutide to evaluate cardiovascular outcomes, which were not required for metformin. Another example is the approvals of first-in-class cholesterol-lowering agents Mevacor (lovastatin) and Praluent (alirocumab), approved by the FDA in 1987 and 2015, respectively. Thirteen clinical trials that enrolled a total of 551 patients were conducted for lovastatin, while alirocumab was studied in nine clinical trials totaling 4,125 patients. The FDA required large, multiyear follow-up trials as conditions of approval for Praluent, which were not required for lovastatin, in order to evaluate cardiovascular outcomes.
[viii] A good understanding of the term *clinical utility* is provided by Patrick Bossuyt et al., "Beyond Diagnostic Accuracy: The Clinical Utility of Diagnostic Tests," *Clinical Chemistry* 58, no. 12 (2012): 1636–43. But we must note that the authors are wrong when they claim (on page 1637) that "safe and effective" is evidently interpreted to mean clinical utility (see on this Gulfo, Briggeman, and Roberts, "The Proper Role of the FDA," 8–10).
[ix] Barbara J. Evans, "The Future of Prospective Medicine under the Food and Drug Administration Amendments Act of 2007," in *FDA in the 21st Century: The Challenges of Regulating Drugs and New Technologies*, eds. Holly Fernandez Lynch and I. Glenn Cohen (New York: Columbia University Press, 2015), 92–105.
[x] Richard Williams, Jason Briggeman, and Ethan C. Roberts, "How Productive Is the FDA's Human Drugs Program?" (Mercatus Center at George Mason University, Arlington, Va., 2016).
[xi] The task of assessing the value of the FDA's work is sometimes complicated by a paucity of information collected by the FDA on its use of funds, its goals, and its accomplishments. See US Government Accountability Office, *Medical Product Oversight: FDA Needs More Strategic Planning to Guide Its Scientific Initiatives* (Report to Congressional Requesters, 2016), http://www.gao.gov/assets/680/677116.pdf.

[xii] See, e.g., Lewis A. Grossman, "FDA and the Rise of the Empowered Patient," in *FDA in the 21st Century: The Challenges of Regulating Drugs and New Technologies*, eds. Holly Fernandez Lynch and I. Glenn Cohen (New York: Columbia University Press, 2015), 71–72.
[xiii] According to Kenneth Getz of the Center for the Study of Drug Development at Tufts University, "The number of new molecular and biologic entities in the R&D pipeline . . . has been rising 7% annually" in recent years. See Kenneth Getz, "The Transformative Promise of Patient Centric R&D," *Clinical Trials Yearbook 2015* (London: Arena International), 59. If maintained, annual growth of 7 percent would result in a doubling of the pipeline within 10 years.
[xiv] Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton, NJ: Princeton University Press, 2010), 750.
[xv] For more on this, see Gulfo, Briggeman, and Roberts, "The Proper Role of the FDA." The FDA increasingly seeks to obtain data, prior to approval, on patient *outcomes* (e.g., whether a patient fully recovers, lives longer, etc.) in order to guess at the clinical utility that a product will have once it is in real-world use. Outcomes-focused trials, which often must be lengthy as well as broad, are far more uncertain in their conclusions than are trials that aim to show safety and effectiveness — that a drug has biological activity related to a disease and is safe to use in that context. Much uncertainty in outcomes-focused trials comes from the many assumptions that are made about how the real-world settings will differ from the controlled trial setting. In the real world, patient responses to drugs often vary wildly as a result of profound heterogeneity in genetics, conditions, and more. But such differences are effectively concealed by the FDA's emphasis on premarket regulation. The amount of variation in patient responses that can be represented in preapproval trials is extremely limited, and so when purporting to assess a drug's clinical utility, the FDA by necessity uses a construct of an "average patient." So even though patient responses — and also patient preferences, such as tolerance for risk — vary greatly, if FDA predicts that its "average patient" will not benefit from a drug, the drug is barred from the medical marketplace. Thus, one practical result of the clinical utility standard is the blocking of many drugs that may provide substantial clinical utility to some patients. The medical marketplace is not allowed to embark on the learning processes that would direct those drugs to the situations in which they could be used beneficially.
[xvi] The FDA's own reputation can and does sometimes decline, with immense consequences; see Carpenter, *Reputation and Power*, chapter 12.
[xvii] One might get an inkling of the vastness and long history of such operations from reading Douglas Whittet, "One Hundred Years of Information on Drugs," *British Medical Journal* 286, no. 6370 (1983): 1032–34.
[xviii] Gulfo, Briggeman, and Roberts, "The Proper Role of the FDA."
[xix] For example, shockingly, the 21st Century Cures Act calls for training FDA staff on one of the most critical bedrock foundations of device law—least burdensome approach—precisely because FDA staff members are not familiar with it. P.L. 114–255, sec. 3058, https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.
[xx] Shannon Gibson and Trudo Lemmens, "Overcoming 'Premarket Syndrome': Promoting Better Postmarket Surveillance in an Evolving Drug-Development Context," in *FDA in the 21st Century: The Challenges of Regulating Drugs and New Technologies*, eds. Holly Fernandez Lynch and I. Glenn Cohen (New York: Columbia University Press, 2015), 268–85.
[xxi] An Associated Press brief on the number of drugs approved by the FDA during 2015 states matter-of-factly, "The rising figures reflect an industrywide focus on drugs for rare and hard-to-treat diseases, which often come with streamlined regulatory reviews, extra patent protections and higher price tags" ("FDA Drug Approvals Climb to Highest Level Since 1996," *New York Times*, January 4, 2016). Regarding reviews, one study finds that, during the last decade, drugs targeting rare diseases had a higher probability of advancing through each phase of the FDA approval processes, resulting in a cumulative "likelihood of approval" more than twice as high as that for all other drugs (David W. Thomas et al., *Clinical Development Success Rates 2006–2015* (Washington, DC: Biotechnology Innovation Organization, 2016), 16–17, https://is.gd/BIOreport.
[xxii] Rosa DeLauro, quoted in Sue Hughes, "Avandia and FDA Both Subject of Severe Criticism at Congressional Hearing," *Medscape*, May 11, 2010, http://www.medscape.com/viewarticle/721624.
[xxiii] FDA, "Rosiglitazone-containing Diabetes Medicines: Drug Safety Communication," December 16, 2015, http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm477601.htm.
[xxiv] Tracy Staton, "GSK's Avandia Is Free and Clear at the FDA, 8 Years After Heart-Safety Controversy Began," *FiercePharma*, December 17, 2015, http://www.fiercepharma.com/pharma/gsk-s-avandia-free-and-clear-at-fda-8-years-after-heart-safety-controversy-began.

[xxv] Harlan Krumholz, quoted in Heidi Ledford, "Drug Markers Questioned," *Nature*, April 1, 2008, https://www.nature.com/news/2008/080401/full/452510a.html.
[xxvi] Geoffrey Levitt, "Drug Safety Communication: The Evolving Environment," in *FDA in the 21st Century: The Challenges of Regulating Drugs and New Technologies*, eds. Holly Fernandez Lynch and I. Glenn Cohen (New York: Columbia University Press, 2015), 328–42.
[xxvii] Connecting Patients to New and Potential Life Saving Treatments, Hearing before the Senate Committee on Homeland Security and Governmental Affairs, February 25, 2016.
[xxviii] See 21 U.S.C. 355(d).
[xxix] Gulfo, Briggeman, and Roberts, "The Proper Role of the FDA."
[xxx] Eric Budish, Benjamin N. Roin, and Heidi Williams, "Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials," *American Economic Review* 105, no. 7 (2015): 2044–85.
[xxxi] Food and Drug Administration, "Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination," June 2013, https://www.fda.gov/downloads/drugs/guidances/ucm236669.pdf; Joseph V. Gulfo and Henry I. Miller, "Needed: An FDA Revolution," *City Journal* (Manhattan Institute, New York, N.Y.), May 2, 2018, https://www.city-journal.org/html/needed-fda-revolution-15882.html.
[xxxii] "The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to: '. . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.'" Food and Drug Administration, *Guidance for Industry: Expedited Programs for Serious Conditions — Drugs and Biologics,* May 2014, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf.
[xxxiii] "IBRANCE is a kinase inhibitor indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. (1) This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial." Ibrance Highlights of Prescribing Information, Pfizer Laboratories, http://labeling.pfizer.com/ShowLabeling.aspx?id=2191, accessed September 4, 2016.
[xxxiv] "KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of:

- patients with unresectable or metastatic melanoma.
- patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials." Keytruda Highlights of Prescribing Information, Merck, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf, accessed September 4, 2016.
[xxxv] John Sotos has suggested a reform along lines somewhat similar to, but ultimately much more radical than, ours. "It's Time to Radically Change How the FDA Approves Drugs," *The Experts* blog, *Wall Street Journal*, June 29, 2016, http://blogs.wsj.com/experts/2016/06/29/its-time-to-radically-change-how-the-fda-approves-drugs/. The similarity lies in the "graded approach" that Sotos's reformed FDA would apply in evaluating new drugs, publishing ratings of drugs that "physicians and patients would use . . . as a starting point." The radical difference is that Sotos proposes that the FDA keep drugs off the market only "in exceptional circumstances," whereas we believe drugs that fail to demonstrate safety and effectiveness should not be approved.
[xxxvi] For basic information on these programs ("there can be confusion about the specific meaning of each and the distinctions among them"), see Food and Drug Administration, "Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review," http://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm.

[xxxvii] Food and Drug Administration, "FDA Commissioner Announces Avastin Decision" (press release, FDA, November 18, 2011), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280536.htm.

[xxxviii] Nick Freemantle, "Interpreting the Results of Secondary End Points and Subgroup Analyses in Clinical Trials: Should We Lock the Crazy Aunt in the Attic?," *British Medical Journal* 322 (2001): 989–91.