

The Proper Role of the FDA for the 21st Century

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ABSTRACT

The FDA’s mission is to permit safe and effective new drugs, biologics, and devices onto the market in an efficient and timely manner. But fear of being blamed for the failings of approved products has caused the FDA to become too restrictive. The FDA has strayed from the safety and effectiveness standards that are set out in the law, instead applying standards for approval that are based on predicting the benefits and risks—clinical utility, disease outcomes, survival—that an “average patient” will experience. But these outcomes are better evaluated in real-world, post-market settings—that is, in the medical marketplace, where knowledge about the value of a drug or device for different types of patients can grow over time. The FDA must return to its role as gatekeeper of safe and effective drugs and devices, and refrain from attempting to anticipate the future judgments of physicians and patients regarding benefits and risks.

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The mission of the Food and Drug Administration (FDA), as stated in the Food, Drug and Cosmetic (FD&C) Act, is “to *promote* health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion.” This includes “ensuring that . . . (B) human and veterinary drugs are *safe and effective*; (C) there is reasonable assurance of the safety and effectiveness of devices intended for human use.”¹

Ultimately, the FDA’s mission is to provide doctors in the medical marketplace with access to safe and effective new drugs, biologics, and devices in a prompt, efficient, and timely manner. The medical marketplace, which involves patients, payers,² and physicians, functions to identify the best products for individual patients. The starting point should be the criteria that doctors, particularly early adopters with the most need for new products in their medical armamentarium, minimally demand to see from new products before they have the confidence to start using them. But the FDA is not asking the doctors what they need; instead, it is trying to encroach on the role of physicians. Why?

In a word, *fear*. This fear stems from unreasonable expectations of perfection from certain segments of society. Fear of being blamed for the failings of approved products has caused the FDA to be too cautious in its reviews and approvals.³ In a sense, the FDA has restated its mission from *promoting* health to *protecting* health, from permitting new products that can advance health to demanding certainty that products will not cause any harm. However, as drugs are small molecules designed to have an effect by binding to targets in

1. See 21 U.S.C. § 393—Food and Drug Administration (2010) (our emphases).

2. Payers are health insurance companies, accountable care organizations, closed provider networks (e.g., Kaiser Permanente), Medicare, and so on.

3. See Vahid Montazerhodjat and Andrew W. Lo, “Is the FDA Too Conservative or Too Aggressive? A Bayesian Decision Analysis of Clinical Trial Design,” August 19, 2015, http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2641547; Alex Tabarrok, “Is the FDA Too Conservative or Too Aggressive?,” *Marginal Revolution*, August 26, 2015, <http://marginalrevolution.com/marginalrevolution/2015/08/is-the-fda-too-conservative-or-too-aggressive.html>.

“When we consider that conflicting studies continue to emerge about health outcomes related to coffee and red wine, which have been in use for thousands of years, we can see the absurdity of expecting the FDA to somehow anticipate, unerringly, all possible health outcomes from the use of new drugs.”

the body, it is impossible to give assurance that no harm will ever occur.

But the expectation from certain areas of society is that the FDA completely vets all potential side effects of new drugs for all people in all situations, even effects resulting from uses that are not intended and are not in conformity with approved labeling. Such an expectation is not just impossible to satisfy—it is entirely unreasonable. When we consider that conflicting studies continue to emerge about health outcomes related to coffee and red wine, which have been in use for thousands of years, we can see the absurdity of expecting the FDA to somehow anticipate, unerringly, all possible health outcomes from the use of new drugs.⁴

Due to fear and pressure from the media, members of Congress, and others, the FDA does not take as its starting point the view of doctors who are on the front lines of patient care. Instead, over the last 20 years the FDA has become markedly more restrictive concerning new drugs, in particular through a focus on its efforts to anticipate clinical outcomes of drug treatment (as opposed to surrogate or intermediate endpoints, amelioration or reduction of signs and symptoms of disease, biomarkers, etc.). The effect of the increased restrictiveness verges on telling doctors how to treat patients, as though the regulators are to prescribe drugs remotely from Silver Spring, Maryland. The FDA is applauded by many, particularly those who have misinterpreted the rise of an academic movement known as evidence-based medicine, when it purports to debunk medical practice on the basis of the humongous clinical trials that it requires drug companies to perform as a condition for approval.⁵ And so the trend has been for the FDA to become more and more restrictive, protracting its

4. Simple searches of the National Institutes of Health’s PubMed research database for “coffee consumption” (<http://www.ncbi.nlm.nih.gov/pubmed/?Db=pubmed&term=coffee%20consumption>) and “red wine consumption” (<http://www.ncbi.nlm.nih.gov/pubmed/?term=red+wine+consumption>) turn up hundreds of studies.

5. Matthew Herper, “Robert Califf Could Transform the FDA—the Right Way,” *Forbes*, September 16, 2015, <http://www.forbes.com/sites/matthewherper/2015/09/16/robert-califf-could-transform-the-fda-the-right-way/>.

pre-approval processes and now frequently requiring that additional controlled trials be done after approval.⁶

As we will show, the FDA is straying, not only from the statutes passed by Congress, but also from its own rules, in guidance documents that are being promulgated; this is how the safety and effectiveness standards have been eroded and changed over time. Despite incessant pleas from doctors and patients for more products that might help when used appropriately, the FDA continues to raise the evidentiary threshold for permitting a new product—recasting premarket approval as a venue for the practice of evidence-based medicine. This move is aimed at satisfying FDA critics, but it consumes precious time and resources, and it dissuades drug developers (and would-be developers) from pursuing projects.⁷

The FDA has acknowledged the changes in its standards for product approval. In a March 10, 2015, opinion piece, two high-ranking FDA officials had this to say about the review process: “It is important to remember, however, that innovative therapies only save lives if they work properly. U.S. citizens rely on the FDA to ensure that the drugs they take are effective and that their benefits outweigh their risks. *Improving a patient’s life or lifespan must be central* to the concept of drug innovation.”⁸ But the FDA is supposed to assure *safety and effectiveness of drugs*, not *life outcomes for patients*. A drug’s label indicates what the drug will have an effect on; safety and effectiveness are to be determined in the context of that labeling. The physician and the patient, acting in the medical marketplace, are to determine whether and when taking the drug will be conducive to improving a patient’s life. That we authorize physicians to prescribe drugs off-label is indicative of this division of labor.⁹ Certainly, studies of life outcomes can be invaluable to informed decision-making by physicians and payers in situations where pointed questions have been developed about a drug’s benefits and risks for patients. But because of the multifactorial nature of disease (the many

6. Michael Dickson and Jean Paul Gagnon, “Key Factors in the Rising Cost of New Drug Discovery and Development,” *Nature Reviews Drug Discovery* 3, no. 5 (May 2004): 417–29.

7. The FDA has noted in one guidance document that “the demonstration of effectiveness represents a major component of drug development time and cost; the amount and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public.” FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998, Clinical 6, 1–2.

8. Janet Woodcock and Karen Midthun, “US Can Continue to Lead in Drug Innovation,” *The Hill*, March 10, 2015, <http://thehill.com/opinion/op-ed/235278-us-can-continue-to-lead-in-drug-innovation> (our emphasis).

9. Kelli Miller, “Off-Label Drug Use: What You Need to Know,” WebMD Feature, accessed January 19, 2016, <http://www.webmd.com/a-to-z-guides/features/off-label-drug-use-what-you-need-to-know>.

and varied factors that contribute to disease development, progression, and response to therapy), it is far harder to produce good knowledge about life outcomes for patients than it is to produce good knowledge about a drug's safety and effectiveness with respect to specific disease-related parameters.

The fact that improved life outcomes for the “average patient” are frequently not proven in trials of drugs that show activity on specific disease parameters and are safe may often have more to do with the multifactorial nature of disease than with the drug. Since studies cannot control for all important disease-modulating factors, proof of disease activity and safety should be sufficient for approval; it should not be necessary to show improved life outcomes. For example, it can be shown in a trial that a drug causes dilation of the bronchial tubes, but it would be extremely difficult or impossible to prove that the drug will improve the lives of a specific cohort of asthma patients. Indeed, it is very often the case that even large, lengthy, and expensive *outcomes* trials produce inconclusive results, so to impose a blanket requirement for such trials—encompassing even those drugs whose safety and effectiveness can be proven and where there is an absence of any definite controversy—will lead to many instances in which useful drugs are needlessly suppressed, causing costs and harms to patients.

The FDA is thus imposing new standards before approval rather than allowing the medical marketplace to determine whether and for whom a new product is a real innovation. This is directly contradictory to the desires of some current legislators, as expressed in the most recent draft of the 21st Century Cures bill, that the FDA consider the individual preferences and experiences of patients.¹⁰ Different patients experience conditions differently, and are willing to accept different levels of risk. An *ex ante* standard of improving the life or lifespan of an “average patient” cannot take this into account.

The shift in regulatory philosophy from promoting health to protecting health has not only increased the cost and time of drug development, it has also moved the FDA from its proper role in making public health decisions to become an improper force driving private health decisions (see table 1). We must change this philosophy in order for medical innovation to deliver on the potential that 21st century science and medicine has to offer. We need to bring the FDA into the 21st century by bringing it back to its roots: assuring drug safety and effectiveness, not outcomes.

10. H.R.6-21st Century Cures Act, 114th Congress (2015–2016), <https://www.congress.gov/bill/114th-congress/house-bill/6>.

TABLE 1. PUBLIC HEALTH VS. PRIVATE HEALTH DECISION-MAKING

Health decision	Public	Private
Primary considerations	safety and effectiveness	benefit/risk
Main question	whether the drug under review can be labeled for safe use under conditions proposed by the drug sponsor	whether the likely benefits outweigh the likely risks of using the drug in the patient presenting to the physician
Responsibility	FDA	physicians in the medical marketplace
Inputs into decision	clinical trial results in regulatory filings	the personal profile of the patient under treatment, drug labeling, personal experience, literature, peer consultation
Contribution of drug intervention to the decision	determination of drug activity (pharmacologic, clinical, patient-reported, biomarker, surrogate endpoints-related) in modulating disease in the “average patient”	clinical outcomes of individual patients treated with the drug: improvements in survival, patient-reported outcomes, reduced morbidity, improved tolerability
Extenuating circumstances	conditions for which no other therapies exist	patient preferences

MEDICAL KNOWLEDGE IS GROWING AND BEING SHARED AS NEVER BEFORE

We are firmly entrenched in the information economy. Consumers can go online, engage in social media, and ask as many friends and followers as possible about cars, appliances, schools, child care, vacations, lawn mowers, kitchen gadgets, and electronics before buying these products and services. Doctors can also access unprecedented amounts of data, and they can do so faster than ever before. They don’t have to wait for the next conference or the next edition of a professional journal—they can share observations and outcomes instantaneously. Patients benefit because the doctor can combine specific knowledge about the individual patient with data on how similar patients responded to treatment. The medical marketplace will never be the same.

Owing to such trends, the future of medicine is at least as exciting as its present. Simple software and hardware can turn a smartphone into a device that can, among other things, diagnose ear infections, distinguish a heart attack from digestive distress, and identify sleep apnea. Data from Internet searches can help the medical community identify previously unknown side effects of medications. These kinds of technological advances make it easier to self-diagnose symptoms and to improve monitoring and communication of vital data, which brings down medical costs to consumers and leads to safer, more rapid, and more effective treatment.

Furthermore, at no other time in history have we been better equipped to perform real-world, large-scale outcomes and survival studies with regard to medical interventions, such as the use of drugs and devices. There is no way

that pre-approval studies of drugs and devices, in tightly defined patient populations under scripted medical management protocols, can produce the kind of evidence that is available through real-world data acquisition and the Internet of Things. What's more, in the post-approval, real-world setting, data that will enhance the selection of therapy for an individual patient can be made available in an unprecedented manner, which can truly drive personalized medicine.

BUT THE FDA, PERHAPS SURPRISINGLY, HAS BECOME MORE RESTRICTIVE

Given the president's 2015 State of the Union address,¹¹ which unveiled the Precision Medicine Initiative designed to give doctors a wider range of tools, knowledge, and therapies to select from when treating patients, one would think that the FDA would embrace the great opportunity represented by the information economy. Regrettably, it hasn't. The FDA has in fact moved away from personalized medicine, increasing its emphasis on trial results for an "average patient" as the standard for permitting new drugs and devices. And even though patients, doctors, hospitals, and payers now have ready access to knowledge about medical products, the FDA has become more restrictive with regard to permitting new drugs and devices.

In large part, it has done so by moving away from what is written in the FD&C Act regarding new applications. This law lists permissible reasons to refuse an application. Specifying reasons for refusal implies that approval is the default position. The safety and effectiveness criteria found in chapter 1 of the law are the most important:

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions. . . .

(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.¹²

11. White House, "Fact Sheet: President Obama's Precision Medicine Initiative," press release, January 30, 2015, <https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative>.

12. C.F.R. Title 21, Chapter 1, Subchapter D, Part 314, Subpart D, § 314.125.

Notably absent in the law is any description of refusing an application on the basis of the FDA's predictions about how benefit-risk assessments will be made by an "average patient" and the patient's physician. The agency has also departed from the statutory language by considering possible uses outside of the labeled uses. The law states that the FDA is to judge a drug's safety, on the basis of "tests" and "investigations," in the context of the "conditions of use prescribed, recommended, or suggested in its proposed labeling." This expressly does not include possible off-label uses.¹³ Yet the FDA now asserts that it "must also consider how people will actually use newly approved drugs once they are marketed," using "methods from social and behavioral science" to anticipate "cognitive and behavioral factors affecting human judgment and decision making in the context of health care delivery."¹⁴ It is now commonplace for FDA guidance documents to stray, not only from the statutes passed by Congress, but also from the FDA's own rules. This is how the safety and effectiveness standards have been progressively eroded and changed over time.

The agency has also become more restrictive by requiring that pre-approval clinical trials be far larger than in the past¹⁵—often enrolling participants in numbers comparable to those seen in epidemiological studies of post-approval use in the population. The goal of such massive pre-approval trials is to obtain data on *outcomes* (that is, whether a patient recovers or lives longer, etc.), in order to guess at the clinical utility that a product will have once it is in real-world use—even though a predicted lack of clinical utility is arguably not a permissible reason to refuse an application.¹⁶

Such outcomes-focused trials, which must be lengthy as well as broad, are far more uncertain in their conclusions than are trials that aim to show that a drug has biological activity related to a disease and is safe to use in that setting.¹⁷

13. C.F.R. Title 21, Chapter 1, Subchapter D, Part 314, Subpart D, § 314.125(b)(2)–(5).

14. FDA, *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA V Implementation Plan*, February 2013, 2.

15. Dickson and Gagnon, "Key Factors in the Rising Cost." The authors note that data from a variety of sources indicate that the length of the process, from synthesis of a compound to approval of a new drug application, has increased, and that this increase is largely due to increases in regulatory requirements, the length of trials, and the complexity of trials.

16. Surrogate endpoints, as opposed to clinical outcomes or scales, were used in fewer than half of the pivotal premarket trials for those novel therapeutic agents that were eventually *approved* during the period 2005–2012. See Nicholas S. Downing et al., "Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012," *Journal of the American Medical Association* 311, no. 4 (2014): 368–77. Generally speaking, comparably systematic data are not or cannot be assembled regarding drugs that remain unapproved.

17. Clifton Leaf, "Do Clinical Trials Work?," *New York Times*, July 13, 2013, <http://www.nytimes.com/2013/07/14/opinion/sunday/do-clinical-trials-work.html>.

For example, a cholesterol drug may safely improve cholesterol levels for a given patient, but a trial may not show the drug to have positive effects on outcomes such as the patient's lifespan. This does not mean, however, that the drug should be denied to all patients it could help. Safety and effectiveness are the measures that the FDA needs to use, as per law, in public health decision-making. And it isn't just safety and effectiveness—the question is whether the drug *can be* labeled for safe use according to the claim submitted. That is, the law in fact instructs the FDA to consider new drugs for approval on the basis of the uses submitted by sponsors (who are responding to the medical marketplace). The FDA should not be telling sponsors that their drugs must show improvement in clinical outcomes; rather, the FDA's role is to label drugs for safe administration in accordance with uses for which they determine the drugs are indeed active. It is then the job of doctors in the medical marketplace to determine the benefits and risks of using new drugs in individual patients, informed by the drug label, their experience with the drug, post-approval studies, and patient factors.

Much of the uncertainty in outcomes-focused trials comes from the many assumptions that are made about how real-world settings will differ from the controlled trial setting. The FDA's use of such assumptions flattens the real world down to the experience of an imagined "average patient." This can mean, of course, that if the "average patient" doesn't surpass certain benchmarks in a trial, the FDA will not permit the drug for use by *any* patient.¹⁸ Yet it is well known that patients often vary dramatically in responsiveness to a given drug, and even though the reasons for such variation are often unknown, the responsiveness itself is often readily observable.¹⁹ Therefore, in the real world a doctor and patient often have the opportunity to try a treatment, observe that it is not working, and switch the patient to another treatment. The availability of additional safe and effective treatment options will often improve the results that doctors and patients obtain by using that routine trial-and-error process.²⁰

18. One useful discussion of the FDA's "average patient" standard is provided in Anup Malani, Oliver Bembom, and Mark van der Laan, "Accounting for Heterogeneous Treatment Effects in the FDA Approval Process," *Food and Drug Law Journal* 67, no. 1 (2012): 23–50.

19. See, e.g., Anthony Y. H. Lu, "Drug-Metabolism Research Challenges in the New Millennium: Individual Variability in Drug Therapy and Drug Safety," *Drug Metabolism & Disposition* 26, no. 12 (1998): 1217–22.

20. Such a process—observation of patient response to treatment, followed by a decision either to switch or not to switch therapies—is commonly incorporated in formal modeling of therapy selection. For one example, see Daniel Carpenter, Justin Grimmer, and Eric Lomazoff, "Approval Regulation and Endogenous Consumer Confidence: Theory and Analogies to Licensing, Safety, and Financial Regulation," *Regulation & Governance* 4, no. 4 (2010): 383–407.

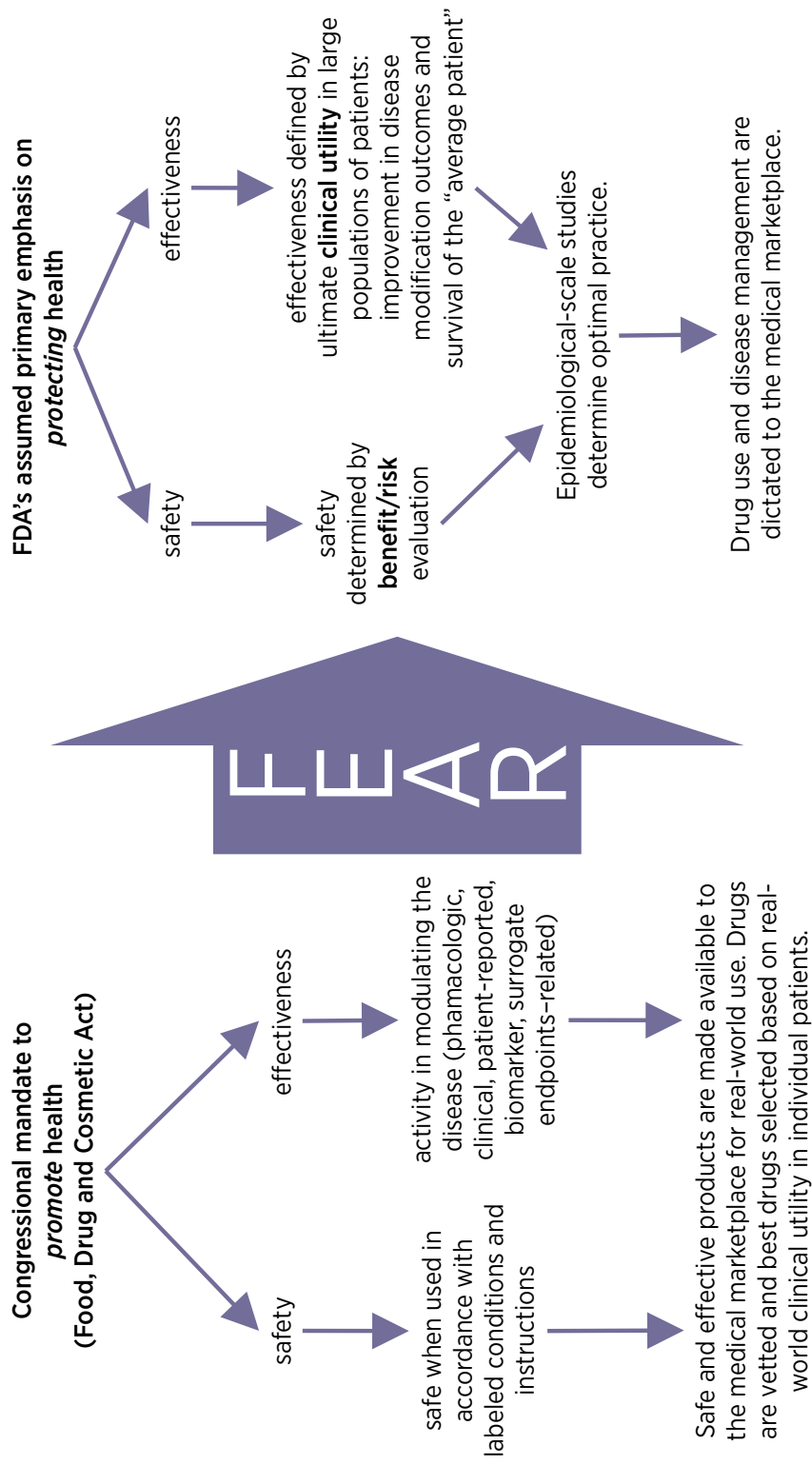
The FDA sometimes imposes another restrictive standard that impedes routine learning processes as well as medical innovation in general: the standard requiring that a new drug demonstrate *superiority* over previously approved drugs in order to be approved. (Imagine if every popular song could only be played on the radio if a panel of judges declared it “better than the Beatles!”²¹) An unintended consequence of the imposition of this standard has been a relative dearth of novel drugs for major diseases that some previously approved products also treat. This scenario is an embodiment of the FDA’s “protect health” mentality, where continuation of the status quo—when there are already, say, one or two drugs available to combat a given disease—is considered better than a changed situation, even when the change in question is *giving patients and physicians access to a drug that is different from existing drugs and comparable in quality*. It hardly needs to be said that such a drug, when tried, would surely be found by some patients to be *more* tolerable or useful than the previously approved alternatives. A given drug will not cause the same side effects in the same intensity for all patients, and so keeping a drug off the market because it is not deemed “superior” in fact *does* deny many individuals access to better drugs—the safe and effective options that would cause fewer or less intense side effects for them. If there were only one birth control pill available, a woman would not be able to find the pill that works best for her. So here is an obvious and frustrating instance of a missed opportunity for the FDA to promote health.

Figure 1 shows the transformation of the FDA approval process because of regulators’ fear. Safety in accordance with labeling becomes safety for an imagined “average patient” with an arbitrarily assigned risk threshold. Effectiveness as identified by activity in modulating

“Imagine if every popular song could only be played on the radio if a panel of judges declared it ‘better than the Beatles!’ ”

21. Credit for the phrase, though applied to consumer decisions as opposed to regulatory decisions, goes to Jack Scannell; see “Four Reasons Drugs Are Expensive, of Which Two Are False,” *Forbes*, October 13, 2015, <http://www.forbes.com/sites/matthewherper/2015/10/13/four-reasons-drugs-are-expensive-of-which-two-are-false/>.

FIGURE 1. FDA REGULATION FOLLOWS PHILOSOPHY



the diseases becomes statistically significant improvements in disease outcomes, requiring very large trials that are all but necessarily longer.

Finally, FDA talk of benefits and risks also creates pressure for comparative effectiveness studies to be brought into the premarket drug approval process. Although “benefit and risk” sounds like a fine construct upon which to make determinations about the usefulness of new drugs, it is not (at least for the FDA). Rather, it ushers in consideration of a new drug’s utility in clinical settings, which leads to a demand for data on hypothetical patient outcomes.²² While clinical trials can show whether a drug is active in modulating disease parameters, however, even the largest trials cannot control for the myriad factors that affect ultimate outcomes. In other words, choosing to base FDA decisions on benefits and risks implies that the FDA will take on the decision roles of physicians and patients, attempting to anticipate or predict their future choices. Requiring comparative effectiveness trials is a logical but unfortunate consequence of such an attempt because someone must choose *among* drugs. Requiring comparative effectiveness trials further adds to the cost and time it takes to develop new drugs. Benefits and risks, and comparative effectiveness, can and should be analyzed post-approval, in the medical marketplace. If certain payers demand comparative effectiveness trials, it need not be an FDA function to oversee such trials.

Increased FDA restrictiveness is also manifest in required post-approval studies. In years past, required post-approval studies were strictly observational, performed to determine whether a safety signal occurred when populations of patients different from those enrolled in the pre-approval clinical trials received newly approved products. Now, the FDA is demanding very large and costly *clinical trials* after approval for some drugs, and if a drug does not meet the endpoints of these additional trials, it may be taken off the market or its labeling may be significantly altered. This amounts to a sort of pharmaceutical double jeopardy, with an attendant chilling effect on investment. Further, reasserting the “average patient” standard after some doctors and patients have found the drug useful to them and incorporated it into their routines seems particularly counterproductive.

One way to measure the effects of FDA requirements is to look at drug development costs. Estimates of total pre-approval costs show that out-of-

22. The word *benefit* naturally leads to the question “to whom?” By contrast, the word *effective* naturally leads one to ask “for what?” Couching the matter in terms of *effectiveness* thus tends to promote a focus on what it is that the drug under study can or cannot do, while couching it in terms of *benefits* tends toward speculative imaginings about patient circumstances (e.g., constructs such as “the average patient”) and other unbounded consideration of matters beyond the regulator’s expertise and awareness.

pocket expenses have increased at a rate well beyond inflation.²³ This is in part due to an increase in the regulatory burden and the greater length and complexity of required trials.²⁴ Even minor changes in FDA requirements, such as narrowing the window for meeting a trial endpoint, can lead to important changes in the pharmaceutical and medical technology sectors.²⁵

Observable changes in R&D spending and drug development time may hint at the problem, but it is likely much larger than this kind of data—or any data—can show. A quote by Sergey Brin, cofounder of Google, illustrates the impossibility of empirically demonstrating the full extent of the problem:

Generally, health is just so heavily regulated. It's just a painful business to be in. It's just not necessarily how I want to spend my time. Even though we do have some health projects, and we'll be doing that to a certain extent. But I think the regulatory burden in the U.S. is so high that I think it would dissuade a lot of entrepreneurs.²⁶

Brin has a record of success, vast resources at his disposal, and a network of connections, which makes it especially concerning that even he voices such a view. If the cofounder of Google perceives the healthcare sector this way, it is probable that there is a significant amount of unseen loss.

The price that priority review vouchers command is further evidence that burdensome regulation has caused harm. Priority review vouchers are regulatory incentives awarded to companies that develop drugs for rare pediatric and tropical diseases; upon approval of these orphan drugs, companies are awarded a voucher that can be redeemed for priority review of any future new drug application, even for drugs that are not intended to treat pediatric or tropical diseases. Priority review vouchers are transferrable—they can be

23. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 151–85.

Christopher P. Adams and Van V. Brantner attempted to replicate this study. They verified the findings and added that their own estimates varied from \$500 million to \$2 billion. "Estimating the Cost of New Drug Development: Is It Really \$802 Million?," *Health Affairs* 25, no. 2 (March 2006): 420–28.

24. Dickson and Gagnon, "Key Factors in the Rising Costs."

25. Bruce Booth and Rodney Zimmel, "Prospects for Productivity," *Nature Reviews Drug Discovery* 3, no. 5 (May 2004): 451–56. The authors note that narrowing the window for meeting an endpoint led many major firms to shift away from developing antibiotics.

26. Sergey Brin, interview by Vinod Khosla, "Fireside Chat with Google Co-founders, Larry Page and Sergey Brin," Khosla Ventures, July 3, 2014, <http://www.khoslaventures.com/fireside-chat-with-google-co-founders-larry-page-and-sergey-brin>.

sold to other companies, and frequently they are.²⁷ On August 19, 2015, United Therapeutics announced that it had agreed to sell a priority review voucher to AbbVie for \$350 million.²⁸ Presumably AbbVie believes that a priority review will lead to cost reductions that exceed the purchase price of the voucher. The expected costs to an entrepreneur of developing a drug or device are clearly quite large. Any possible venture that does not involve even larger expected benefits will not be pursued—and there is, of course, no systematic data on projects that never started.²⁹

WHY HAS THE FDA BECOME MORE RESTRICTIVE?

Fear of making a mistake is the major driving force of the FDA's mission creep and increasingly onerous pre-approval requirements. In 1974, FDA Commissioner Alexander M. Schmidt said, "In all of FDA's history, I am unable to find a single instance where a congressional committee investigated the failure of FDA to approve a new drug. But the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. The message to FDA staff could not be clearer."³⁰ In subsequent years the FDA was sometimes criticized for slow approvals or for reducing innovation, but still today the strong perception is that congressional criticism has created within the FDA an "underlying motto": "never do what's best, when you can do what's safe."³¹ Reviewers, burned from the recalls of Vioxx, Meridia, Rezulin, and others, have made life easier for themselves by requiring larger studies focused on outcomes and event rates, and even on proving negatives (that a drug doesn't cause a particular effect). They seemingly have decided that the best way to avoid

27. Alexander Gaffney and Michael Mezher, "Regulatory Explainer: Everything You Need to Know about FDA's Priority Review Vouchers," Regulatory Affairs Professionals Society, July 2, 2015, <http://www.raps.org/Regulatory-Focus/News/2015/07/02/21722/Regulatory-Explainer-Everything-You-Need-to-Know-About-FDA%E2%80%99s-Priority-Review-Vouchers/>.

28. United Therapeutics, "United Therapeutics Corporation Agrees to Sell Priority Review Voucher to ABBVie for \$350 Million," press release, August 19, 2015.

29. The market price for a priority review voucher has risen rapidly. In May 2015, Sanofi paid \$245 million to Retrophin, and in November 2014, Gilead Sciences bought a voucher from Knight Therapeutics for \$125 million.

30. While Schmidt's oft-quoted characterization was a slight exaggeration, at the time of his statement it was essentially accurate. See Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton, NJ: Princeton University Press, 2010), 337–40, especially table 5.6 up to 1974.

31. Tom Coburn, quoted in Hanna Krueger, "Ex-Sen. Coburn: Congress 'Beats the Crap' Out of FDA," *The Hill*, July 14, 2015, <http://thehill.com/policy/healthcare/247911-ex-sen-coburn-congress-unfairly-beats-the-crap-out-of-fda>.

criticism is to require near certainty before approval.³² There has been much less pressure on them to avoid a different type of error—the error of over-caution, which leads to more victims of diseases who might have been helped by drugs that have been suppressed.³³ Such victims are often faceless and voiceless because the public generally cannot know what has been lost due to over-caution.

A second cause of the FDA’s move away from the statute is the increasing influence, starting around 1990, of certain strands of an academic movement called “evidence-based medicine” (EBM). Evidence in various forms was of course already central in most medical decision-making, and appropriate systematic attention to improved application of evidence is to be cheered.³⁴ A sophisticated understanding of EBM allows that both researchers’ production of guidelines *and* physicians’ individual decision-making are inevitable and necessary, that the two must work in tandem, and that evidence has relevance to both.³⁵ For example, *evidence* in the context of physician decision-making can refer to evidence about guidelines themselves—for example, evidence on which guidelines to trust, on when to use them, on how to interpret them, and so forth.³⁶ But some have misinterpreted the advent of evidence-based medicine as representing an abrupt paradigm shift.³⁷ This misinterpretation sometimes manifests itself in disparagement of pre-EBM practices in the medical marketplace as being representative of an unscientific “art of medicine.” In the extreme, the term evidence-based medicine has been used pejoratively to insinuate that—in the current EBM era—physicians and other caregivers can, and should, have little role in decision making. In light of the strength of the EBM movement, it seems reasonable to interpret, say, FDA insistence on outcomes studies as an EBM-inspired vote of mild to little confidence in physicians and the medical marketplace.

32. Joseph V. Gulfo, *Innovation Breakdown: How the FDA and Wall Street Cripple Medical Advances* (Franklin, TN: Post Hill Press, 2014), 239–44.

33. The distinction between cautiousness and safety is similar to the distinction between protecting health and promoting health, discussed above. On such distinctions see Aaron Wildavsky, *Searching for Safety* (New Brunswick, NJ: Transaction Publishers, 1988).

34. Jeffrey A. Claridge and Timothy C. Fabian, “History and Development of Evidence-Based Medicine,” *World Journal of Surgery* 29 (2005): 547–53.

35. David M. Eddy, “Evidence-Based Medicine: A Unified Approach,” *Health Affairs* 24, no. 1 (January 2005): 9–17.

36. “So many parties have jumped on the EBM bandwagon and so many clinical practice guidelines are churned out by individuals, professional organizations, insurers, and others that the benefits of uniformity may disappear in the cacophony of overlapping, conflicting, and poorly constructed guidelines. With more than 1,000 guidelines created annually, calls for ‘guidelines for clinical guidelines’ have been issued.” Stefan Timmermans and Aaron Mauck, “The Promises and Pitfalls of Evidence-Based Medicine,” *Health Affairs* 24, no. 1 (January 2005): 18–28.

37. Earl P. Steinberg and Bryan R. Luce, “Evidence Based? Caveat Emptor!,” *Health Affairs* 24, no. 1 (January 2005): 81, 91n1.

It is true that certain lines of the EBM literature, such as the evidence on geographic variations in medical practice, have pointed strongly to a conclusion that the medical marketplace can err, in the sense of falling short of a standard or ideal. However, there is also little to no evidence that using the FDA premarket approval process to anticipate adoption decisions is a relatively superior approach.³⁸ Health economists Anup Malani and Tomas Philipson have put this point very bluntly:

Economists have conducted relatively little theoretical or empirical research on the efficiency of FDA policies. Ironically, if a product application were presented to the FDA with the scant amount of evidence that currently exists on the efficiency of the policies of the agency itself, such an application would likely be rejected on the basis of insufficient evidence.³⁹

Their point is only strengthened when one notes that Malani and Philipson are speaking about premarket approval per se, and not necessarily with regard to a particularly restrictive variant.

THE GATEKEEPER AND THE MEDICAL MARKETPLACE

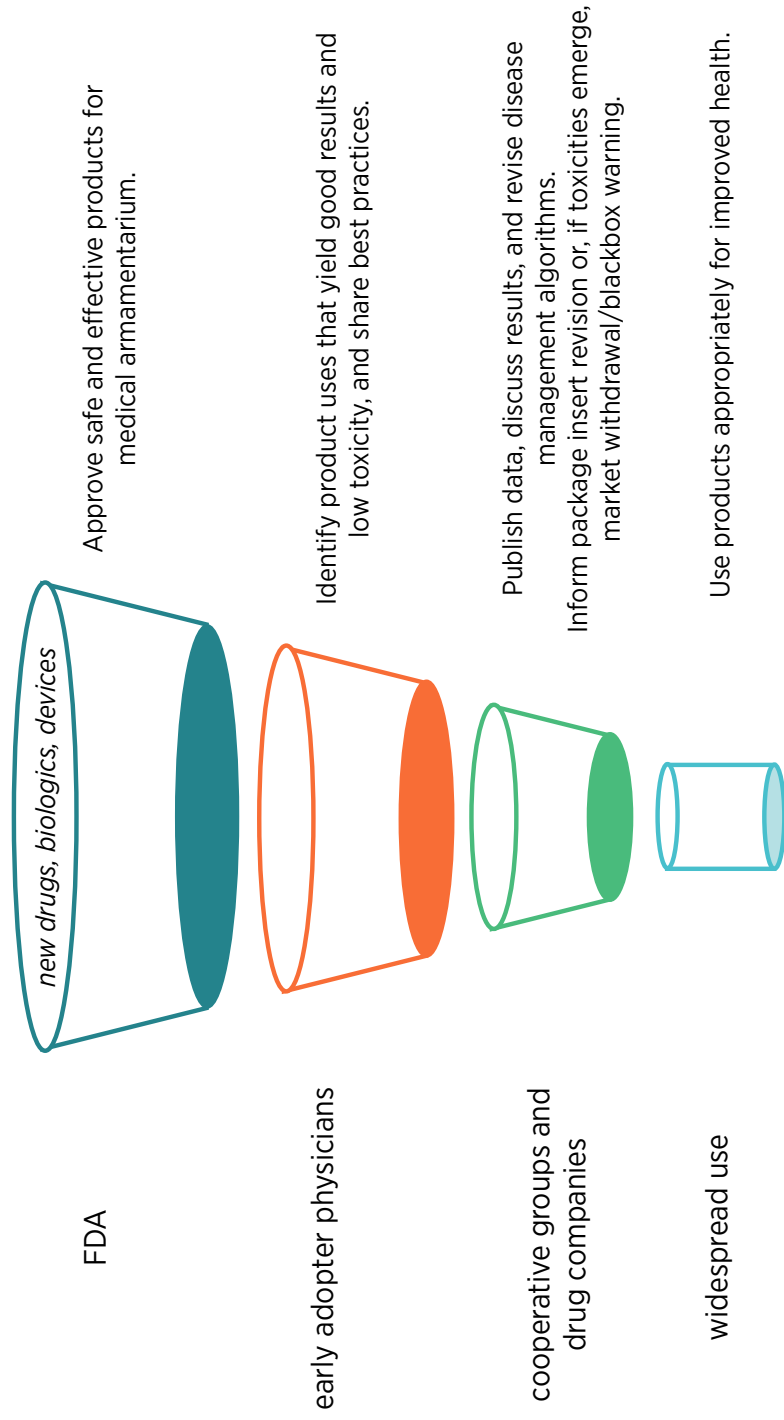
Figure 2 shows the FDA's appropriate role as gatekeeper to the medical marketplace, which is how it functioned in the 1980s and early 1990s. Regulators helped the medical community by approving safe and effective products. Then, as described above, physicians, patients, and payers in the medical marketplace identified the best products for individual patients through a process not unlike natural selection: the drugs that offered the best clinical results for appropriate patients were used preferentially.

In the 1980s and early 1990s—that is, before the current period of increased restrictiveness—the standard used by the FDA in determining whether a drug was sufficiently effective was more about observing the drug's pharmacologic activity on a disease, and less about attempting to anticipate the drug's clinical utility. Rather than endpoints such as survival or fewer bad medical outcomes (e.g., heart attacks, strokes, amputations, or

38. Jason Briggeman, *Searching for Justification of the Policy of Pre-market Approval of Pharmaceuticals*, Ph.D. diss., George Mason University, 2015.

39. Anup Malani and Tomas Philipson, "The Regulation of Medical Products," in *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, ed. Patricia M. Danzon and Sean Nicholson (Oxford, UK: Oxford University Press, 2012), 101.

FIGURE 2. THE MEDICAL MARKETPLACE IN THE 1980s AND EARLY 1990s



progression of disease), trials routinely used surrogate and intermediate endpoints (e.g., fasting glucose levels, blood pressure, tumor shrinkage, and stress tests).⁴⁰

How was clinical utility assured? It flowed out of the medical marketplace. The FDA of the 1980s and early 1990s knew its place in the medical ecosystem to be that of a gatekeeper of new products entering the medical armamentarium. The FDA's role was to *permit* drugs, biologics, and devices based on safety and efficacy (reasonable assurance of safety and effectiveness for medical devices), and then the medical marketplace would *adopt* the best treatments from among those permitted by the FDA, for use by individual patients. The agency was at the top of the funnel, making sure that only safe and effective products passed through. As they still are today, doctors were assigned responsibility for authorizing and guiding patient use of prescription-only drugs, and also as they are today, doctors were empowered and expected to prescribe drugs off-label when appropriate.⁴¹

How were decisions to adopt drugs made? How was personalized medicine exercised? Mostly, such decisions were based on real-world experiences of doctors treating patients and by additional clinical trials sponsored by cooperative clinical groups (e.g., National Institutes of Health), hospital networks, and the biopharmaceutical and medtech industry. This information would be shared at medical meetings and in the literature. Doctors who observed a patient experiencing an idiosyncratic adverse response would switch that patient to an alternative treatment.⁴² In a natural selection process, doctors and patients would learn the best treatment for individual medical situations

“The FDA of the 1980s and early 1990s knew its place in the medical ecosystem to be that of a gatekeeper of new products entering the medical armamentarium.”

40. Russell Katz, “Biomarkers and Surrogate Markers: An FDA Perspective,” *Journal of the American Society for NeuroTherapeutics* 1, no. 2 (April 2004): 189–95, doi: 10.1602/neurorx.1.2.189.

41. Alexander T. Tabarrok, “Assessing the FDA via the Anomaly of Off-Label Drug Prescribing,” *Independent Review* 5, no. 1 (Summer 2000): 25–53.

42. G. R. Venning, “Validity of Anecdotal Reports of Suspected Adverse Drug Reactions: The Problem of False Alarms,” *British Medical Journal* 284 (1982): 249–52.

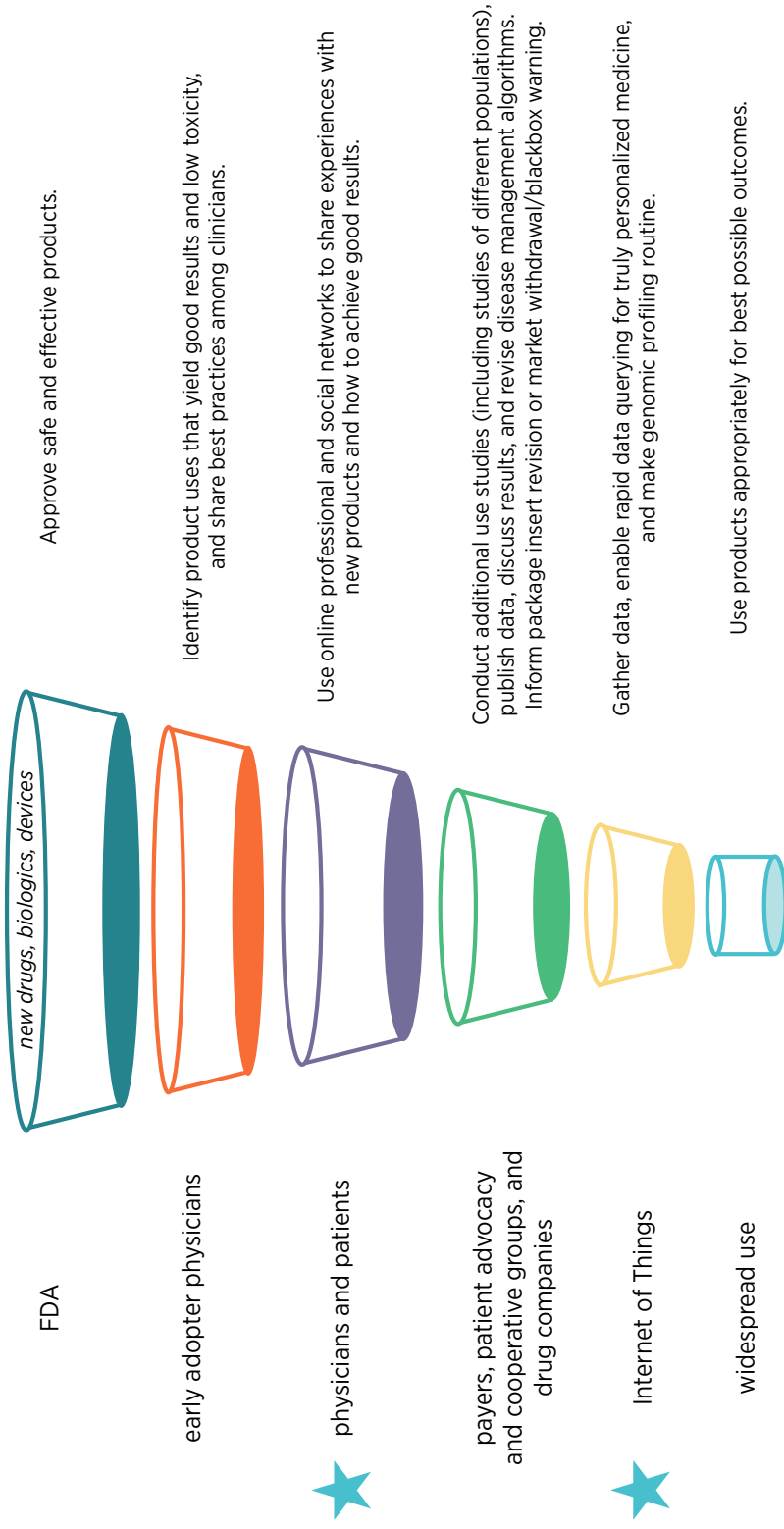
and use the appropriate drugs and devices in the medical armamentarium. This narrowed the funnel by identifying optimal uses of available safe and effective products. More often than not, these pearls of wisdom, even as they were codified in practice guidelines and medical pathways, would never make it into the package insert (that is, the labeling approved by the FDA). The ability of today's medical marketplace to vet approved products and drive the adoption of those that have the greatest clinical utility is greatly strengthened by the emergence of online patient and doctor communities for immediate sharing of knowledge and best practices. The FDA itself has acknowledged the power of the Internet by partnering with Google to use search terms and topics as a means of identifying new information about drugs.⁴³

We believe that a reinvigorated medical marketplace system, with the FDA returned to its proper role at the top of the funnel, could help realize the promise of the information economy and personalized medicine for 2015 and beyond. FDA premarket approval is designed to deliver an initial permission decision; postmarket controls are aimed at modifying drug labels, or even withdrawing the drugs, if issues emerge in their use in the medical marketplace. *Adoption* decisions do, and should, vary over time as more is learned in clinical practice, additional trials, and epidemiological research. With knowledge so much more readily available to doctors, drugs should again be permitted on the basis of safety and effectiveness—and not rejected on the pretense that, by invoking a mythical “average patient,” the FDA can credibly wrap all future adoption decisions into its permission decision. Prescription requirements remain a viable means of restricting patients' access to drugs that are difficult to use appropriately and as directed.

Figure 3 shows the FDA at the top of the new and more dynamic medical marketplace, in its proper role of permitting safe and effective drugs onto the market. It also shows how the information economy and the ability to rapidly share and process data help doctors improve patient outcomes at a rate and scope previously not possible. The new marketplace better assures that appropriate treatments are provided to patients.

43. Michael Mezher, “FDA and Google Talk ‘Adverse Event Trending,’” Regulatory Affairs Professional Society, July 16, 2015, <http://www.raps.org/Regulatory-Focus/News/2015/07/16/22888/FDA-and-Google-Talk-Adverse-Event-Trending/#>.

FIGURE 3. THE MEDICAL MARKETPLACE AS IT SHOULD BE TODAY



REASONS TO REINVIGORATE THE ROLE OF THE MEDICAL MARKETPLACE

Why should we go “back to the future” in this way? Why will this system be better? We believe an important element of the answer is that doctors believe it will help patients. And, patients want their doctors to try to help them more—that is what Right to Try laws, approved now in 24 states, are all about.

Physicians and Patients Should Have More Options More Quickly

What do early adopters want to see from the FDA approval process before they start the real-world use of drugs, knowing that drug studies do not directly correlate with individual patient experiences?

1. They want products that have been evaluated in a manner that gives them confidence to prescribe drugs safely and in accordance with appropriately labeled conditions of use and instructions. In addition, they want to see data demonstrating that new compounds have activity in clinical parameters of importance to them and to their patients. Statistically significant assessments of safety, as well as data supporting the pharmacologic activity of new drugs (surrogate markers, intermediate endpoints, symptom relief, resolution or improvement of clinical signs of disease) are required prior to use by early adopters. Definitive evidence of improvement in disease outcomes and survival is not required.
2. There has been an inexorable progression toward greater and greater data demands by the FDA before approval. This greatly impedes the development of products for diseases that affect large segments of the population in favor of niche diseases, hurts patients by delaying products that can provide medical benefit, and adds to the time and cost of trials. Doctors need more drugs to treat diseases that affect millions of Americans.
3. Unfortunately, today’s FDA often requires unequivocal evidence of clinical utility to be demonstrated before approval. While the doctors are in support of having as much data as possible to inform their treatment decisions, there is no doubt that some doctors feel that post-approval studies performed by industry, as well as independent clinical investigators, are well-suited for providing evidence of clinical benefit. Moreover, they want to see clinical benefit for themselves, or they will not continue to use the drugs.
4. There are many examples of the FDA having denied approval, or having inhibited further development, of drugs that would make valuable

additions to the current medical armamentarium. Doctors want more safe and effective products that can help their patients.

Table 2 shows the minimum amount of information physicians need for several medical conditions in order to make choices with their patients, both immediately after the release of new drugs and after the drugs have been in the medical marketplace for a while. In summary, before using new drugs, doctors who are early adopters want to know that drugs can be safely administered, have pharmacologic activity, and, in some cases, have shown a hint or trend (rather than statistically significant proof derived from epidemiologic-scale studies) of improving disease outcome parameters. Definitive proof of clinical utility and outcomes or survival before approval is not necessary and unduly delays or holds back important new medicines that doctors want to use in some of their patients. The appendix contains additional discussion about the medical conditions and the development efforts of drugs to treat the diseases highlighted in the table.

The FDA's Expanded Role Has Created Economic Problems

Economic analysis can shed light on unintended consequences of the FDA's increasing restrictiveness and imposition of an outcomes-focused standard. Here we focus on two growing problems, both of which can be addressed by a reinvigoration of the medical marketplace model.

Increased restrictiveness has denied patients good alternatives to older drugs. There are many drugs in the current armamentarium that were approved back when there were smaller and much less rigorous trials. The FDA keeps these on the market (generally appropriately), while often refusing to approve drugs that are being developed *in today's world, with today's biomarkers and assessments, and today's brand of transparent rigorous trials*. We should, all else being equal, probably favor drugs that were developed more recently even if they demonstrate only comparable safety and effectiveness, rather than superior performance. Drugs developed in recent times have been characterized to a much greater extent (commensurate with discoveries and advances in basic biology, laboratory methods, genomics, and medicine) compared to drugs developed 15 to 30 years ago. However, by supplanting *safety* with benefit-risk and *effectiveness* with clinical utility and outcomes, the FDA has moved the goalposts, with the ironic result that older drugs have been protected from newer would-have-been competitors, even in instances when the clinical usefulness of the older drugs has faded.

TABLE 2. MINIMUM INFORMATION PHYSICIANS NEED TO MAKE DRUG CHOICES

Condition	Premarket, informational needs of early adopters	Postmarket additional data welcomed to further inform therapy selection
Prostate cancer treatment	<ol style="list-style-type: none"> Phase 2 data: biomarker response (drop in PSA), tumor shrinkage (radiologic evidence), patient-reported outcome improvement (bone pain), and progression-free response exceeding literature. Safe to use in accordance with label. Approval for use when standard therapies fail. (The FDA often requires survival outcomes for full approval.) 	<ol style="list-style-type: none"> Phase 3 & 4 studies conducted by pharma companies with early adopters. When available, data on outcomes (progression-free and overall survival), as well as on broader safety experience, are to be disseminated. Widespread use dependent on the extent to which doctors' experiences mimic clinical trial data.
Cardiovascular diseases:		
Hypercholesterolemia	<ol style="list-style-type: none"> Reduction in LDL cholesterol. Safe to use in accordance with label. (The FDA often requires cardiovascular outcomes—reduction in myocardial infarction, stroke, etc. —to be initiated as conditions of approval.) 	<ol style="list-style-type: none"> Expanded safety and tolerability data. Head-to-head outcomes studies to decide which agents will be used preferentially. Additional studies in subgroups and special populations.
Hypertriglyceridemia	<ol style="list-style-type: none"> Reduction in triglyceride levels to within (or near) normal limits, especially in patients at high risk of bad cardiovascular outcomes. Safe to use in accordance with label. (The FDA often requires a reduction in frequency of major cardiac events.) 	<ol style="list-style-type: none"> Expanded safety and tolerability data. Head-to-head outcomes studies to decide which agents will be used preferentially. Additional studies in subgroups and special populations.
Low HDL levels	<ol style="list-style-type: none"> Increased HDL levels in patients at high cardiovascular risk. Increased HDL levels (irrespective of baseline cardiovascular risk) including a non-statistically significant trend showing improved cardiovascular outcomes. Safe to use in accordance with label. (The FDA often requires cardiovascular outcomes—reduction in myocardial infarction, stroke, etc. —as conditions of approval.) 	<ol style="list-style-type: none"> Expanded safety and tolerability data. Head-to-head outcomes studies to decide which agents will be used preferentially. Additional studies in subgroups and special populations.
Metabolic Diseases:		
Hyperuricemia (elevated uric acid levels)	<ol style="list-style-type: none"> Reduction in uric acid levels to within (or near) normal limits, especially a rising uric acid level. Safe to use in accordance with label. (The FDA requires reduction in uric acid in patients with gouty arthritis as the basis for approval.) 	<ol style="list-style-type: none"> Expanded safety and tolerability data. Data on attacks of gouty arthritis and tolerability relative to other approved agents will help decide which products are used in selected patients.
Diabetes	<ol style="list-style-type: none"> Reduction in serum hemoglobin A1c levels. Safe to use in accordance with label. (The FDA often requires HgbA1c reductions and large outcomes studies to prove that the drugs do not increase risk of negative cardiovascular outcomes as conditions of approval.⁽⁶³⁾) 	<ol style="list-style-type: none"> Expanded safety data to include effect (positive or negative) on cardiovascular outcomes, and to determine if toxicities or negative outcomes can be managed or reversed by other means if hypoglycemic effect is substantial. Demonstration of improved cardiovascular outcomes, as seen with Jardiance, will increase breadth of use.⁽⁶⁾ Additional studies in subgroups and special populations.

continued on next page

Condition	Premarket informational needs of early adopters	Postmarket additional data welcomed to further inform therapy selection
Female health:		
Vaginal atrophy	<ol style="list-style-type: none"> 1. Improvement in functional endpoints (e.g., dryness, vaginal wall thickness, for example) and a pooled basket of patient reported outcomes (pain, dyspareunia, and dysuria). 2. Safe to use in accordance with label. (<i>The FDA often requires large clinical trials in each symptom, separately: pain, dyspareunia, and dysuria.</i>) 	<ol style="list-style-type: none"> 1. Expanded safety and tolerability data. 2. Head-to-head functional and outcomes studies to decide which agents will be used preferentially.
Infection	<ol style="list-style-type: none"> 1. Increased acidity of vaginal secretions—brought to near premenopausal levels with reduced colonization of coliform bacteria and yeast. 2. Safe to use in accordance with label. (<i>The FDA often insists on clinical utility outcomes, for example, reduction in pyelonephritis, which requires study of tens of thousands of patients.</i>) 	<ol style="list-style-type: none"> 1. Expanded safety and tolerability data. 2. Head-to-head functional and outcomes studies to decide which agents will be used preferentially.
Sexual desire	<ol style="list-style-type: none"> 1. Increased desire, satisfaction, and sexual episodes. 2. Safe to use in accordance with label. (<i>The FDA often additionally requires large outcomes studies to prove that testosterone-based drugs do not increase risk of negative cardiovascular outcomes as conditions of approval.</i>) 	<ol style="list-style-type: none"> 1. Expanded safety and tolerability data. 2. Head-to-head functional and outcomes studies to decide which agents will be used preferentially.
Osteoporosis	<ol style="list-style-type: none"> 1. Studies showing improvement in bone mineral density in nonvertebral areas (hips and wrists) combined with reductions in vertebral fracture. 2. Safe to use in accordance with label. (<i>The FDA often requires large clinical studies of reduction in nonvertebral fractures.</i>) 	<ol style="list-style-type: none"> 1. Expanded safety and tolerability data. 2. Head-to-head functional and outcomes studies to decide which agents will be used preferentially.

(a) Boaz Hirshberg and Arie Katz, "Cardiovascular Outcome Studies with Novel Antidiabetes Agents: Scientific and Operational Considerations," *Diabetes Care* 36 (2013): S253–58.
(b) Ron Winslow, "New Diabetes Drug Shows Sharply Reduced Risk of Heart-Related Death," *Wall Street Journal*, September 17, 2015, <http://www.wsj.com/articles/new-diabetes-drug-shows-sharply-reduced-risk-of-heart-related-death-1442528430>.

“The reason the FDA had approved no other oral drugs to treat methicillin-resistant SSSI was largely that it had been requiring *superiority* to active treatment as the criterion for approval, which is very difficult to demonstrate.”

The antibiotics crisis—a host of health problems caused by emerging bacteria that resist treatment by approved antibiotics—is a prime example.⁴⁴ Zyvox⁴⁵ (linezolid), an antibiotic granted approval by the FDA in 2000, was “the only oral drug approved for complicated SSSI (skin and skin structure infections) caused by methicillin-resistant *Staphylococcus aureus* (MRSA)” until 2014. The reason the FDA had approved no other oral drugs to treat methicillin-resistant SSSI was largely that it had been requiring *superiority* to active treatment as the criterion for approval, which is very difficult to demonstrate. (Further, it is unethical to force patients into a treatment to which they are knowingly resistant for the sake of a clinical trial—that is, a treatment that is certain to provide no benefit to them—in order to show superiority, a situation that can often complicate clinical trials.)

To address these issues, the Qualified Infectious Disease Product (QDIP) designation program, passed as part of the 2012 Prescription Drug User Fee Act (PDUFA) reauthorization (FDA Safety and Innovation Act), allowed for fast track approval of antibiotics for serious or life-threatening infections, including those caused by an antibacterial- or antifungal-resistant pathogen, which permitted the demonstration of non-inferiority—rather than superiority—to active treatment as the endpoint for clinical trials to support approval. Following this, Sivextro⁴⁶ (tedizolid) was approved in 2014 by demonstrating non-inferiority to linezolid. Unfortunately, outbreaks of linezolid-resistant strains of *Staphylococcus aureus* had by then been occurring for several years.⁴⁷ In general, over

44. See, e.g., Frances Weaver, “The Antibiotics Crisis,” *The Week*, November 16, 2013, <http://theweek.com/articles/456340/antibiotics-crisis>.

45. Pfizer, Highlights of Prescribing Information: Zyvox, last modified July 2015, <http://labeling.pfizer.com/ShowLabeling.aspx?id=649>.

46. Merck, Highlights of Prescribing Information: Sivextro, last modified July 2015, http://www.merck.com/product/usa/pi_circulars/s/sivextro/sivextro_pi.pdf.

47. Philippe Prokocimer et al., “Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections,” *Journal of the American Medical Association* 309, no. 6 (2013): 559–69.

this period the problem of antibiotic resistance had continued to grow while the flow of new antibiotics diminished.

The “average patient” standard is disfavoring drugs for large-population diseases. The “average patient” standard as applied in outcomes-focused trials has caused a burgeoning of narrow, niche claims.⁴⁸ Once the domain, rightfully and appropriately, of rare pediatric diseases such as enzyme deficiencies, targeting narrow diseases is now a preferred development pathway for even the largest companies because of the FDA’s implicit and explicit incentives, such as priority review vouchers, Breakthrough Therapy designation, Fast Track review, and Accelerated Approval.

Could these incentives cause companies to abandon pursuit of drugs to treat diabetes, heart failure, obesity, chronic obstructive pulmonary disease, addiction, early-stage cancer, and other diseases with massive numbers of patients? For claims of effectiveness in those diseases, the FDA may require clinical trials with tens of thousands of patients, assessing not only disease outcomes but also survival.⁴⁹ Meanwhile, for narrow, niche claims—which are often created by simply taking refractory (disease recurrence despite prior treatment) populations or those with a specific mutation—the FDA requires comparatively very little in the way of testing. Not only are required trials smaller and thus less costly for niche drugs, there is also a lower bar for approval. Recall that—unfortunately—the FDA often considers “the benefits and risks of *other available therapies*” when making approval decisions on new drugs.⁵⁰ But a maker developing a niche drug, where there are no available therapies, doesn’t have to worry about the FDA attempting to estimate the drug’s value compared to existing drugs. Furthermore, the specificity of a niche drug assures its good performance in an “average patient,” and there is a limited number of patients that would be exposed should the drug turn out to be more toxic than originally thought. For all these reasons, the final decision to approve a niche drug is often a no-brainer.⁵¹ The FDA loves to tout

48. Joseph V. Gulfo, “Corrupting the Common Cure,” *Economic Intelligence, U.S. News & World Report*, April 27, 2015, <http://www.usnews.com/opinion/economic-intelligence/2015/04/27/fdas-orphan-drug-designation-warps-medical-research>.

49. See, e.g., Malorye Allison, “Can Cancer Clinical Trials Be Fixed?,” *Nature Biotechnology* 29 (2011): 13–15.

50. FDA, *Structured Approach to Benefit-Risk Assessment* (our emphasis).

51. Drugmakers are also explicitly incentivized to develop niche drugs. The FDA uses rewards such as priority review vouchers and extended periods of market exclusivity to induce makers to develop drugs for rare diseases. The Breakthrough Therapy designation, made law in 2012, provides regulatory incentive for developers to pursue drugs that address significant unmet medical needs, including niche, refractory claims. And there are new incentives for niche product development in the 21st Century Cures bill.

niche-drug approvals and wants them to weigh heavily in evaluations of FDA performance (i.e., PDUFA)—and Congress has generally let the FDA get away with it.⁵²

The FDA Should Pay Heed to the Spirit of the Law

We believe that the system of the 1980s and early 1990s was more in keeping with the law than is the more restrictive regime the FDA now imposes. Back then, Congress limited FDA consideration of a drug’s effectiveness to the effect represented on the proposed labeling.⁵³ Congress intended drug developers to conduct clinical trials and submit applications for uses of their products that they see fit, assuming that market forces would drive the selection of meaningful and appropriate endpoints in order for their products to compete. Drugs were meant to be safe when used as labeled, and to have some activity in modulating a targeted clinical parameter. FDA approval was not to be interpreted as meaning that a drug could be supposed risk-free for an “average patient” or as meaning that a drug’s efficacy had been measured relative to other drugs.⁵⁴ But in practice, it is the FDA that tells companies what is and is not appropriate evidence, and today’s FDA has moved away from pharmacodynamics activity, surrogate markers, and intermediate endpoints to survival and major health outcomes. Companies have no choice but to listen.

The increased sophistication and efficiency of today’s medical marketplace in carrying forward a natural selection process to arrive at the best products for appropriate patients should give us confidence in reasserting the spirit of the law as described above. In particular, the capability and importance of payers in assessing medical value has grown enormously. Payers have a very strong incentive to select from among the safe and effective products those that are of the greatest medical value—that is, the ones that provide health

52. If FDA review performance were meeting goals set out in the law—such as the goal of 10 months for a standard new drug application review—some niche-drug exclusivity incentives (see previous note) could be reduced or dropped. But for true orphan diseases, e.g., congenital enzyme deficiencies, exclusivity inducements will still be needed.

53. C.F.R. Title 21, Chapter 1, Subchapter D, Part 314, Subpart D, § 314.125(b)(5).

54. Another important benefit from returning to more tightly defined standards for safety and effectiveness would be enhanced precision of the informational function served by an FDA approval decision. That is to say, the meaning of an approval—what a drug’s approval by the FDA says (and does not say) about the drug—has been muddled by the greater uncertainty inherent in outcomes-focused trials and the application of the “average patient” concept. On the importance of public understanding of the meaning of a drug’s approval by the FDA, see Lisa M. Schwartz and Steven Woloshin, “Communicating Uncertainties about Prescription Drugs to the Public: A National Randomized Trial,” *Archives of Internal Medicine* 171, no. 16 (2011): 1463–68.

outcomes that are satisfactory to physicians and patients. Large payers, particularly Centers for Medicare and Medicaid Services, often demand—and sometimes sponsor—post-approval studies that provide evidence on outcomes, which give assurance to late adopters or cause early adopters to reconsider. Furthermore, a marketplace with multiple payers tends to mitigate negative impact from any idiosyncratic obstinacy on the part of the regulator. When there are multiple payers, there are multiple opportunities for innovative products to be studied and appreciated, and then later more widely adopted, perhaps even by a stubbornly closed-minded payer once others have validated the value of the intervention. A similar dynamic, of course, applies with regard to physicians: early adopters use the products first, and then late adopters may or may not follow.

CONCLUSION: CONGRESS SHOULD ACT TO DEFINE FDA STANDARDS FOR SAFETY AND EFFECTIVENESS

The good news is that the fix for mission creep is quite easy: Congress can guide the FDA back to the letter and spirit of the FD&C Act by more explicitly defining safety and effectiveness. Doing so can prevent the FDA from dictating to the medical marketplace how new drugs, biologics, and devices should be used to help individual patients. There are several steps Congress can take to put the FDA back in its proper role:

1. Explicitly limit the FDA to considering the safety of intended uses, according to the label. FDA reviews should not be permitted to speculate about the safety of off-label uses or of uses in populations beyond those the label indicates.
2. Define safety with regard to the likelihood of causing death, debilitation, or severe harm. This definition would focus FDA reviewers on filtering out the most dangerous drugs and allow the medical marketplace to determine appropriate uses for medicines that might be blocked under a more restrictive safety threshold. Such a definition is aligned with the fact that individuals experience conditions differently, and it places the focus on whether the drug can be labeled in such a way as to promote its safe administration, in accordance with the law.
3. Define effectiveness as having positive activity on the disease (amelioration or reduction of signs and symptoms, surrogate endpoints, biomarkers, etc.).
4. Require the FDA to expand its use of surrogate endpoints (including biomarkers) in trials and reviews. This should include specific, actionable

targets so that the FDA can be held accountable by the public if it fails to take action.

Congress should couple these reforms to the law with a strengthened norm against undue criticism of the FDA by Congress. Risk cannot be eradicated from the use of drugs, and human foresight is limited; therefore poor outcomes cannot by themselves justify the placing of blame for those outcomes upon the FDA. Whenever the FDA is assiduous in following the law and acting appropriately on the knowledge available at the time, then it is to be supported. Congressional leaders should vocally affirm such a norm in order to reduce the fear that has led the FDA to a stance of excessive cautiousness and protraction.

The FDA has an integral role in the medical marketplace as arbiter of appropriately defined safety and effectiveness, but the FDA's judgment with respect to safety and effectiveness clearly has gone awry. Congress must act to address this so that the other constituents of the ecosystem can perform their roles in order to ensure that the best products for each individual patient are used in a manner that will enhance the health of all Americans in a prompt, efficient, and timely fashion.

APPENDIX: EXAMPLES OF THE IMPROPER ROLE OF THE FDA IN DRUG DEVELOPMENT AND REVIEWS OF NEW DRUG APPLICATIONS

The FDA's efforts to dictate to the practice of medicine and to supplant the medical marketplace in determining the most appropriate use of drugs for individual patients are very apparent in the development requirements it imposes on drug companies and the labeling restrictions it places on new products. This section highlights recent examples in which safety and effectiveness were not the primary focus of the FDA. In these examples, the FDA assumed the role of the medical marketplace by demanding data on clinical utility, clinical benefit, and disease outcomes as conditions of approval.

Hypercholesterolemia

Hypercholesterolemia is a particularly interesting example because it demonstrates the FDA's approach to surrogate markers, the use of which it does not support as the basis of product approvals in other than narrow or niche disease populations.

The finding that LDL cholesterol reduction leads to improved survival has been shown in numerous landmark studies of several different drugs (e.g, pravastatin, atorvastatin, rosuvastatin) over the last 20 years. Why must new drugs to reduce cholesterol be made to show improved survival? With all of the studies that have been performed on multiple different compounds, if LDL lowering is not a good surrogate for cardiovascular outcome, the concept of surrogate endpoints is hollow.

At the June 2015 FDA Advisory Committee meetings for evolocumab (Repatha by Amgen) and alirocumab (Praluent by Sanofi and Regeneron), both monoclonal antibodies directed against a new target in cholesterol synthesis, impressive data demonstrating dramatic LDL reductions were reviewed. The FDA approved the products on the basis of LDL lowering for very high-risk patients, but is withholding approval for broader patient populations until the studies on survival and cardiovascular outcomes (major cardiovascular events, abbreviated MACE) are completed and positive. Many in the medical community are not in support of withholding that approval:

“I was really focused on the very large unmet medical need in patients who are high risk,” said panel member Dr Philip Sager (Stanford University School of Medicine, San Francisco, CA) in explaining his “yes” vote. “It's more likely than not this drug

will actually be able to reduce cardiovascular outcomes. I do acknowledge the uncertainty in not knowing what the cardiovascular outcomes will actually show, but I was unwilling to wait until 2017 or 2018 to get those results.”⁵⁵

Michael H. Davidson, MD, FACC, FNLA, professor and director of the lipid clinic at the University of Chicago Pritzker School of Medicine, said more populations should have been recommended for immediate indication. “I was disappointed that the panel did not recommend approval for statin intolerance, which is difficult to define, but from a patient perspective is clearly a real issue,” he said. “The FDA panel vote is a sober reminder that there are many skeptics who want outcome trials before utilizing these very effective and well-tolerated agents.”⁵⁶

The European Commission approved Amgen’s Repatha (evolocumab) to treat patients with uncontrolled cholesterol who need intensive low-density lipoprotein cholesterol reduction, which includes statin-intolerant patients.⁵⁷ The FDA approved Praluent and Repatha only for patients with cardiovascular disease who need more help getting their cholesterol under control, including sufferers of a rare genetic disorder called familial hypercholesterolemia, but didn’t indicate Praluent and Repatha for statin-intolerant patients.⁵⁸

Heart disease is the leading cause of death in the United States. One would think that the FDA would want to get as many safe and effective drugs on the market as possible in order to reduce the number of deaths due to heart disease. However, rather than accepting proof that a drug reduces LDL, the FDA withholds approval for the general population until drug makers have conducted longer and more expensive studies. As any student of Economics

55. Michael O’Riordan, “Approve PCSK9 Inhibitor Evolocumab, FDA Panel Recommends,” *Medscape.com*, June 10, 2015, <http://www.medscape.com/viewarticle/846236>.

56. Erik Swain and Adam Taliercio, “FDA Advisory Panel Backs Approval of PCSK9 Inhibitors,” *Cardiology Today*, July 2015, <http://www.healio.com/cardiology/chd-prevention/news/print/cardiology-today/%7Ba48c08c5-0d4d-4cb2-8706-010ee8a95886%7D/fda-advisory-panel-backs-approval-of-pcsk9-inhibitors>.

57. Joe Barber, “Amgen’s First-in-Class Cholesterol-Lowering Therapy Repatha Approved in EU,” *FirstWord Pharma*, July 21, 2015, <http://www.firstwordpharma.com/node/1300683>.

58. FDA, “FDA Approves Praluent to Treat Certain Patients with High Cholesterol: First in a New Class of Injectable Cholesterol-Lowering Drugs,” news release, July 24, 2015, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm>; FDA, “FDA Approves Repatha to Treat Certain Patients with High Cholesterol,” news release, August 27, 2015, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460082.htm>.

101 knows, increasing costs leads to less of a given action. Increase the costs to drug makers of marketing cholesterol drugs, and they will make fewer cholesterol drugs.

Correction of Metabolic Derangements

Metabolic derangements are medical conditions manifested in abnormal laboratory tests, initially, which if untreated can lead to clinical manifestations, such as cardiovascular disease or diabetes. While doctors are often appropriately loath to “treat lab tests,” intervening to normalize grossly abnormal laboratory parameters is good medicine in most circumstances. It seems clear, however, that the FDA will not approve drugs based on their effects on these laboratory endpoints alone. Metabolic derangements include correction of serum uric acid, triglyceride, HDL cholesterol, and glucose abnormalities.⁵⁹ Most diseases are quite complex, so it is extraordinarily difficult to conduct trials that, amid the multiple factors that simply cannot be controlled, can ferret out clinical benefits resulting from the correction of derangements. So when clinical benefit is made the standard for approval, doctors and patients are denied access to compounds that both correct derangements and are safe when used as labeled. Following are two examples of these conditions and drugs that treat them.

Hypertriglyceridemia

When Amarin Pharmaceuticals sought to obtain approval for use of Vascepa in patients with elevated triglyceride levels (above 200 mg/dL), the FDA required the company to perform a study demonstrating significant triglyceride lowering and to recruit at least half the patients in a cardiovascular outcomes study (reduction in MACE, including myocardial infarction, stroke, and death).⁶⁰ The company filed a new drug application in compliance with the directive from the FDA, but the FDA then expanded the requirements, stating that it now wanted to see the results of the outcomes study as a condition of

59. Joel Schiffenbauer, “Gout: Clinical Review and Trial Design Issues” (presented at the FDA Arthritis Advisory Committee, June 3, 2004), http://webcache.googleusercontent.com/search?q=cache:T36lOVOhWYAJ:www.fda.gov/ohrms/dockets/ac/04/slides/2004-4044S2_01_Schiffenbauer.ppt+&cd=2&hl=en&ct=clnk&gl=us.

60. Triglycerides are a type of fat, and excessive levels are associated with a risk of heart disease. Approximately one-fourth of Americans have elevated triglycerides. See Margaret D. Carroll, Brian K. Kit, and David A. Lacher, “Trends in Elevated Triglyceride in Adults: United States, 2001–2012” (NCHS Data Brief No. 198, Centers for Disease Control, May 2015).

approval. Medical experts made the case to the FDA that the drug should be approved at this time for lowering triglycerides (even if not for reducing risk of cardiovascular outcomes in patients with triglyceride levels above 200 mg/dL) for a very practical reason: patients with triglyceride levels above 200 mg/dL are often taking fish oil supplements on their own. However, the supplements are not of definite composition and quality, and they often have impurities that are deleterious to patients' health. This common-sense argument did not sway the FDA.

But on August 7, 2015, in their ruling on Amarin's lawsuit against the FDA, the federal courts stated that the company "may engage in truthful and non-misleading speech promoting the off-label use of Vascepa." Now, Amarin is permitted to market Vascepa for use in patients with triglyceride levels above 200 mg/dL under its First Amendment rights to free speech.⁶¹ The FDA has not amended its policies in light of the Amarin decision.

Low HDL Cholesterol

Low HDL cholesterol is a known risk factor for patients with cardiovascular disease, but the FDA has not approved drugs that raise HDL cholesterol despite the fact that several agents have been shown to be effective at doing so. Niacin, for example, increases HDL; however, it was not shown to decrease MACE outcomes. Many doctors believe this was due to confounding issues in the trial, and—since niacin is available—such doctors use niacin to increase HDL.

Drugs of a new class called CETP (cholesterol ester transfer protein) inhibitors have shown significant effectiveness in raising HDL. On October 12, 2015, Eli Lilly announced that the development of its CETP inhibitor, evacetrapib, was stopped even though there were no safety issues because the trial was unlikely to show a reduction in cardiovascular events, as determined by the independent data-monitoring committee. This is unfortunate because there is no telling how this drug may have been shown to be beneficial when used in the real world. The FDA's insistence on cardiovascular outcomes data obscures the medical imperative of raising HDL and the potential benefits that could be assessed in actual use and in post-approval studies in subpopulations of patients with low HDL levels.⁶² Nevertheless, if HDL cholesterol can be increased safely

61. Thomas M. Burton, "Amarin Wins Off-Label Case against FDA," *Wall Street Journal*, August 7, 2015, <http://www.wsj.com/articles/amarin-wins-off-label-case-against-fda-1438961747>.

62. The studies of CETP inhibitors are flawed in the sense that the CETP inhibitors are administered on top of optimum statin therapy; it is likely that the effect of raising HDL is partly masked in the studies by the benefits conferred by lowering LDL.

and reliably, why shouldn't agents be approved so that doctors in the medical marketplace can determine clinical utility in their patients, especially upon review of subgroup analyses and trend identification from pre-approval studies and large post-approval studies?

Prostate Cancer

The circumstances surrounding the use of Taxotere (docetaxel) in prostate cancer also shed light on the medical marketplace in action and on what doctors need to see before early adopters use new drugs. This particular drug was originally approved in 1996 for breast cancer.⁶³ A Phase I/II trial in prostate cancer in 34 patients, published in 1999, demonstrated a 50 percent decline in PSA (prostate specific antigen) and five partial responses (significant reduction in the size of tumor lesions); 8 of 15 patients were able to discontinue narcotic analgesics use for bone pain.⁶⁴

Unfortunately, it was not until two phase III studies of Taxotere *versus* mitoxantrone in hormone refractory patients were conducted that Taxotere was approved for use treating prostate cancer patients on May 19, 2004. A statistically significant survival advantage (18.9 months versus 16.5 months) was demonstrated.⁶⁵

The six-year delay in Taxotere's approval for use on prostate cancer so that improved *survival* could be demonstrated made no sense, given that the drug was approved for use on breast cancer in 1996 and there was strong evidence of its activity on prostate cancer in 1998.⁶⁶ Luckily, Taxotere was given a compendium listing by Medicare, so there was a tremendous amount of off-label use of the drug occurring in the medical marketplace before the accumulation of survival outcomes data:

A study on the diffusion of use of Taxotere in medical practice demonstrated that broader use of Docetaxel [Taxotere] preceded

63. Taxotere (Docetaxel), CenterWatch, accessed January 21, 2016, <https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/110/taxotere-docetaxel>.

64. Daniel P. Petrylak et al., "Phase I Trial of Docetaxel with Estramustine in Androgen-Independent Prostate Cancer," *Journal of Clinical Oncology* 17, no. 3 (March 1999): 958–67.

65. "FDA Approval for Docetaxel," NIH National Cancer Institute, last modified March 28, 2014, <http://www.cancer.gov/about-cancer/treatment/drugs/fda-docetaxel>.

66. The American Cancer Society estimates that there will be over 200,000 new cases of prostate cancer in the United States in 2015 alone. See "How Many Men Get Prostate Cancer?," American Cancer Society, January 30, 2015, <http://www.cancer.org/cancer/prostatecancer/overviewguide/prostate-cancer-overview-key-statistics>.

phase III evidence for its efficacy, indicating extensive off-label use.⁶⁷

The off-label use of Taxotere in the medical marketplace was a very good thing, but how many more patients could have benefitted had the FDA approved Taxotere for use when ample evidence of its potential had been accumulated years in advance?

Female Health

The FDA's extreme caution is evident even after drugs are approved and have been on the market for years. Take, for example, combination hormonal contraceptives (birth control pills, rings, and patches). These products are so safe that California and Oregon have announced that they will be made available over the counter despite their current FDA prescription drug labeling. That labeling contains very frightening language (called "class labeling") conveying safety concerns, particularly for women who smoke and who are over 35 years of age. However, the condition that contraceptives prevent—that is, pregnancy—also poses risks, often much greater ones. The FDA's labeling does not include fair balance because it fails to report on the risk of similar adverse outcomes from pregnancy. In short, the FDA doesn't conduct proper risk-risk analysis.

67. Joseph M. Unger et al., "The Diffusion of Docetaxel in Patients with Metastatic Prostate Cancer," *Journal of the National Cancer Institute* 107 (2015): dju412.

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