

Tiered Orders of FDA Approval Based on Evidence of Effectiveness

General Description of Issue

In 1962, Congress passed the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act), which authorized the FDA to require drug companies to conduct and submit tests determining safety and efficacy prior to approval for marketing. In addition, the FDA now had to preclear all

human trials. This occurred in response to thalidomide-induced birth defects that were observed in the drug's use in 46 countries; interestingly, the drug was not approved for use in the US as the FDA was investigating neurological toxicities during its review of the approval application (continued on pg. 2)...

Purports To Do

1. The safety and effectiveness standard is meant to ensure that new drugs and biologics are not snake oil, that is, that they demonstrate activity in treating a disease, and can be labeled for safe use.
 - a. The effectiveness requirement for (continued on pg. 2)...

Success in Achieving Objective: 5 (0 to 5)

Unintended Consequences

By granting the FDA power to adjudicate safety and effectiveness as the basis of approval, Congress allowed the agency to exercise judgment based on benefit/risk. In doing so, the law set the stage for the FDA to demand an ever-increasing level of effectiveness to offset safety concerns, especially when the agency's decisions (continued on pg. 3)...

Emergence of Unintended Consequences: -4 (0 to -5)

Potential Positive Impact on Innovation

To the extent that marketers of drugs were required to demonstrate an actual biological effect of new products prior to obtaining FDA approval, the changes to the law largely prevented the marketing-driven abuses and science-deficient rationale that propels the supplements (continued on pg. 2)...

Positive Impact on Innovation: 3 (0 to 5)

Potential Negative Impact on Innovation

The vicious cycle leads to an imbalance between premarket requirements and postmarket vigilance. When faced with a Congress that seeks to blame the FDA when toxicities emerge from the use of approved products, the FDA may be said to pursue three courses of reaction: (continued on pg. 4)...

Negative Impact on Innovation: -3 (0 to -5)

MI³ Score =

+1



The requirement that drugs, biologics, and devices be shown to be safe and effective has a net positive effect on medical innovation. However, the use of the clinical utility standard in lieu of effectiveness significantly stifles medical innovation and personalized medicine. We propose changes to the approval process that address the unintended consequences and negative impacts, and could bring the composite score to +8.

Discussion

The law requires that FDA conduct reviews that assure safety and effectiveness when a product is used as labeled; however, it does not require evidence of purported clinical utility. Clinical utility is an elusive standard—it is tantamount to proving that there are, in some (continued on pg. 6)...

Recommendations

Affirm safety and effectiveness as the only requisite standards for approval of new drugs and biologics. For devices, the tenets of reasonable assurance of effectiveness and least burdensome approach must be reinforced and followed.

As often happens when a bureau has (continued on pg. 7)...

General Description of Issue (continued from pg. 1)

submitted in 1960. Still, the horror of seeing truncated limbs resembling flippers in newborns resulted in the passage of the amendments, which significantly expanded the power of the FDA as well as its size – staff increased from one thousand members in 1951 to nearly sixty-five hundred two decades later.

The goal of the effectiveness standard was to make certain that “snake oil,” that is, a drug with no biological activity in a disease, was not entered into the medical armamentarium. Regrettably,

over the years, the FDA has amassed even greater power and authority as it has sought to redefine effectiveness to mean clinical utility, a highly personal measure best determined by doctors and patients. In many cases, drug activity (for example, shrinkage of tumors) is no longer good enough to satisfy effectiveness requirements, rather, long-term health outcomes, including survival are the preferred measures of effectiveness mandated by the FDA. Is this good for medical innovation? ■

Purports To Do (continued from pg. 1)

*drug approval was added to the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) in 1962. Between passage of the Act in 1938 and the 1962 amendments, drug manufacturers were required to show only that their drugs were safe. The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices. After two years of hearings on these issues, Congress adopted the 1962 Drug Amendments, which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." Substantial evidence was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that **the drug will have the effect it purports or is represented to have under the conditions of use***

prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

2. For devices, the [reasonable assurance of safety and effectiveness](#) standard also ensures that new devices provide evidence of biological activity.
 - a. *Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. After considering the nature of the device and the rules in this section, the Commissioner will determine whether the evidence submitted or otherwise available to the Commissioner is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.* ■

Potential Positive Impact on Innovation (continued from pg. 1)

and nutraceuticals market – [for every person who takes a supplement](#) that's medically warranted, experts say more of us are taking something because our neighbor or colleague swears by it. [Over the last decade, sales of vitamins](#), minerals, and nutritional and herbal supplements (VMHS) have surged and many new companies have entered the space. Globally, the market is now valued at \$82 billion, with roughly 28 percent of that in the U.S., where sales increased by approximately \$6 billion between 2007 and 2012. Growth is expected to remain strong through 2017 – between 5 and 6 percent a year both globally and in the U.S.

Supplements are usually made up of a vitamin, mineral or

other nutrient in a higher dose than we would get from food. "Too much of just about any nutrient is a problem," said Dr. Tod Cooperman, president of ConsumerLab.com, a White Plains, N.Y.-based independent firm that tests supplement quality and tracks research on nutritional products. Those who do take supplements shouldn't exceed the dose recommended on the bottle, Cooperman said. Federal oversight of supplements is less stringent than it is for prescription drugs. Supplement manufacturers generally do not have to prove the safety and effectiveness of their product before it is sold to the public. Consumers should also keep in mind that most [\(continued on pg. 3\)](#)...

Potential Positive Impact on Innovation (continued from pg. 2)

supplement formulas on the market have not been clinically tested as packaged by the manufacturer, Cooperman said.

Although market incentives are strong for drug companies to develop novel, differentiated products with significant and

measurable biologic activity, the effectiveness standard helps to guard against the development of drugs with no discernible activity. As, such, these laws have provided incentives for true medical innovation. ■

Unintended Consequences (continued from pg. 1)

are called into question by the media and Congress because of toxicities observed with approved drugs. Congressional oversight should have prevented the FDA from demanding greater proofs of effectiveness beyond biological activity in a disease (e.g., clinical utility and long-term health outcomes), but it has not. In fact, poor Congressional oversight has contributed to the inexorable acceleration of the problem.

Unfortunately, of the [oversight that Congress has conducted in the past](#), much has been of a pernicious form. Wise, fair “police patrol” oversight by Congress would hold the FDA accountable for failure to dutifully carry out the law, that is, enforcing the effectiveness standard as it was intended – to prevent snake oil from entering the market. But often Congress has conducted “fire alarm” oversight—generally 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.

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. Even when the FDA does the right thing—for example, approving an excellent drug that helps millions of patients—it is castigated and publicly humiliated. 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?”

Subsequently, the FDA removed the restrictions from the label when the drug was shown not to cause increased cardiovascular problems, following a reanalysis of a very large prospective study that rendered the meta-analysis flawed. But the damage was done: The FDA changed the regulations to require larger and larger clinical trials and disease outcome endpoints for products that are intended for large chronic diseases, like diabetes.

In [December 2015, the FDA noted](#) the following: “Continued monitoring” of Avandia, Avandamet and Avandaryl had turned up “no new pertinent safety information” about the drugs. So, the agency lifted the final layer of safety measures that it erroneously imposed. But sales of the drug were 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.”

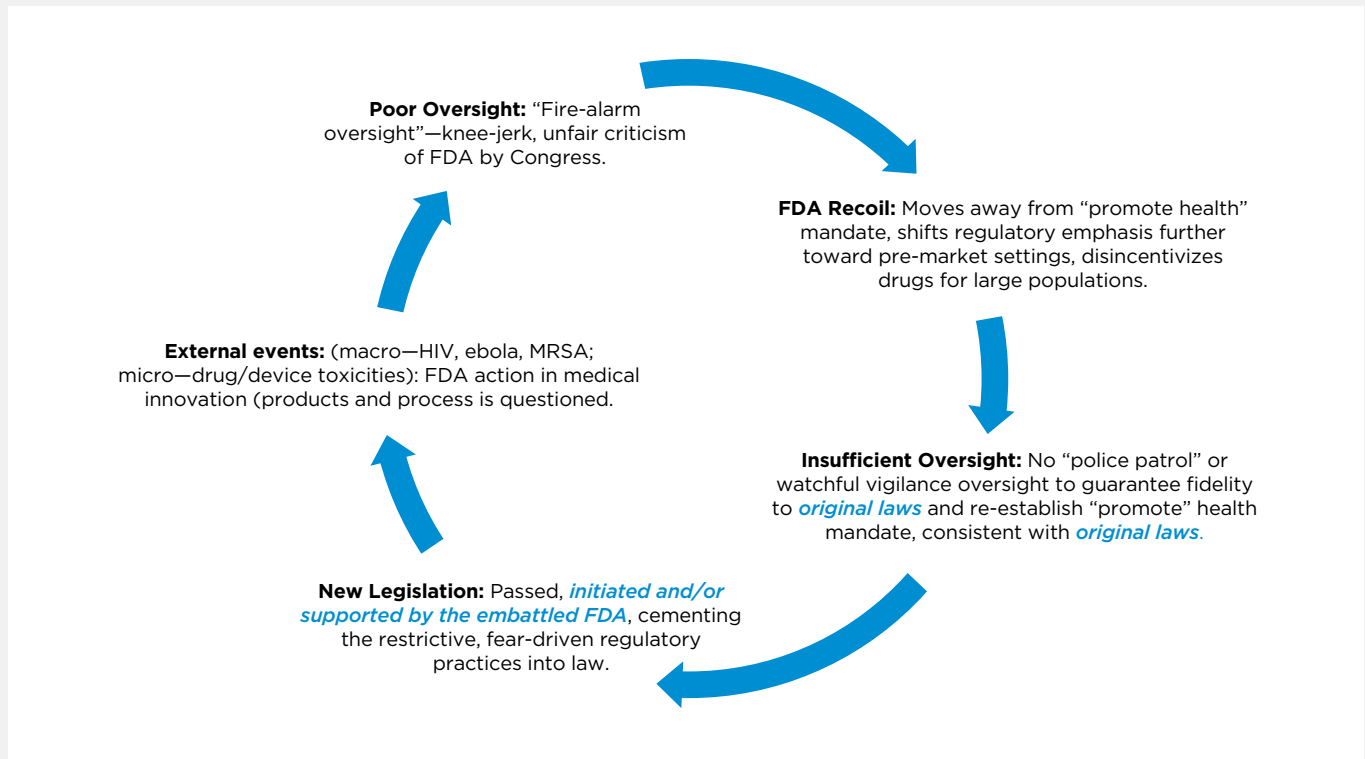
Congress’s failure to conduct the good “police patrol” form of oversight compounds the problem of the FDA’s deviation from the law in reaction to “fire alarm” oversight. After the “fire” is smothered, Congress does not “police” the FDA to bring its practices back in line with the law; it does not re-instruct 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 a priority review for breakthrough devices and many other provisions), which largely focus on orphan conditions, those affecting fewer than 200,000 patients per year.

The following figure 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) and adverse events of approved products call into [\(continued on pg. 4\)](#)...

General Description of Issue (continued from pg. 3)

- 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 as opposed to postapproval vigilance and a migration of the approval standard from effectiveness to clinical utility.
 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. ■

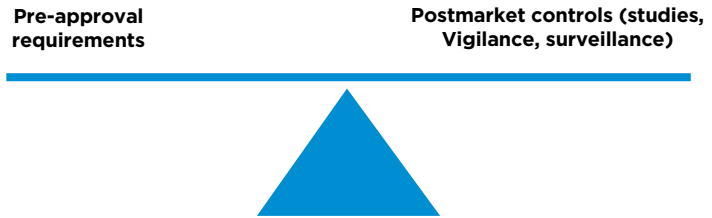


Potential Negative Impact on Innovation (continued from pg. 1)

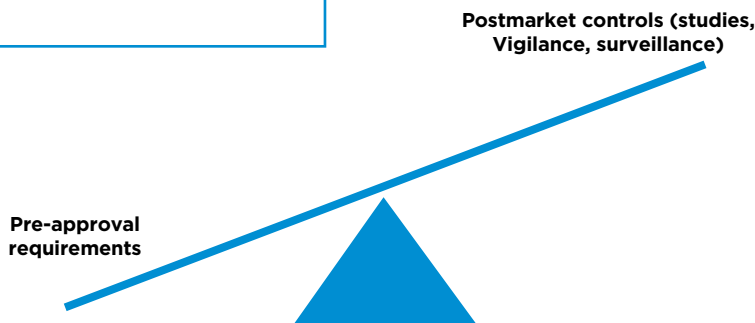
1. The FDA moves its regulatory emphasis further toward preapproval requirements, as opposed to postmarket controls—exacerbating an imbalance that Shannon Gibson and Trudo Lemmens term “premarket syndrome”—thereby adopting a “protect health” posture, at the expense of its “promote health” mandate as defined in the law.
- a. The following figure demonstrates how the balance of preapproval requirements and post-approval controls shifts with each turn of the vicious cycle. It also demonstrates how the nature of the pre-approval requirements and post-approval controls are modulated. [\(continued on pg. 5\)...](#)

Potential Negative Impact on Innovation (continued from pg. 4)

FDA law provides a balance between pre-approval requirements and postmarket controls



Balance between pre-approval requirements and postmarket controls is lost as the vicious cycle turns



- Pre-approval drug, biologic, and device studies longer, larger, and more expensive
- Race toward niche claims and regulatory incentives (Orphan Drugs, Breakthrough Therapy, Fast Track, Priority Review, Accelerated Approval)
- Postmarket requirements remain, with clawback - if survival and disease outcome endpoints not met, can remove from market even if still "effective"
- Fewer approvals of drugs affecting diseases that affect millions of Americans - less innovation where it can have the most impact.

2. The FDA restates approval standards, shifting from safety and effectiveness—based on substantial evidence that the drug will have the effect it purports or 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—291 of them in 2014—and approvals for niche specialty claims in recent times.

- 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 patient

protections and higher price tags.”

- Regarding reviews, one recent 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.

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.

“Average patient” trials ignore individual patient benefits. In order to provide definitive proof of effectiveness, large clinical trials with appropriate statistical power must be conducted - these must show that the average patient receiving the experimental treatment met the effectiveness endpoint to a greater degree than the average patient who received the alternative therapy. The fact that [\(continued on pg. 6\)](#)...

Potential Negative Impact on Innovation (continued from pg. 5)

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, as opposed to 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. ■

Discussion (continued from pg. 1)

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” with regard to 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 is 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 specific promised action. 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 and patients would then make judgments of the clinical utility of the therapies in the real world. And, they would be [free to use the drugs “off label”](#) because safety and effectiveness in at least one claim had been proven.

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 in individual patients. 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.

A shift in US 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 a resilience strategy in medical innovation, which advocates for decentralized trial-and-error based learning with safe and effective products. 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 programs 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 [\(continued on pg. 7\)...](#)

Discussion (continued from pg. 6)

whether a drug has clinical utility, with the result that clinical utility is insufficiently studied in the postmarket setting and is instead mistakenly presumed to exist.

The appropriate division of labor is for the FDA to assure safety and effectiveness, while the ongoing responsibility to tackle questions of clinical utility rest 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 government agency has somehow already done all the work. 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 to enter safe and effective products into the medical armamentarium. ■

The Medical Marketplace As It Should Be Today



Recommendations (continued from pg. 1)

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 many 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 emphasis from a balance of preapproval requirements and postapproval vigilance, such that preapproval requirements now dominate the regulatory paradigm.

These 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.

It should be affirmed that the FDA is [\(continued on pg. 8\)](#)...

Recommendations (continued from pg. 7)

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. A possible 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.

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.

1. *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.
2. *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.
3. *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.
4. *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, diagnostics, and devices is shown in the following tables.
(continued on pg. 9)...

Recommendations (continued from pg. 8)

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 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

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 / Modification

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 and Survival

Improvement in survival; reduction on major cardiac events (myocardial infarction, heart failure, rehospitalization); etc.

(continued on pg. 10)...

Recommendations (continued from pg. 9)

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 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.

<p>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</p> <p>Examples:</p> <ol style="list-style-type: none"> 1. Measurement above a threshold is associated with disease recurrence 2. Rising level is associated with progression of disease 	<p>Category 2: Predicts safety and effectiveness in patients receiving drug/biologic therapy</p> <p>Examples:</p> <ol style="list-style-type: none"> 1. Companion diagnostics 2. Test correlates with drug/biologic effect, taken during drug therapy to determine whether <ul style="list-style-type: none"> (a) continued treatment is likely to be safe, or (b) clinical response is likely (clinical signs and symptoms, disease modulation, clinical outcomes and survival) 	<p>Category 3: Predicts for disease presence or progression</p> <p>Examples:</p> <ol style="list-style-type: none"> 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.) 	<p>Category 4: Information provided by the test induces interventions that favorably alter the natural history of the disease</p> <p>Examples:</p> <ol style="list-style-type: none"> 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
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Recommendations (continued from pg. 10)

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 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.

Physical Action		Clinical Sequelae	
<p>Category 1: Tools - used in conjunction with diagnostic or therapeutic intervention (surgery or drug delivery)</p> <p>Examples:</p> <ol style="list-style-type: none"> Used to help conduct or facilitate diagnostic or therapeutic procedures 	<p>Category 2: Used to diagnose disease, to provide treatment, or to repair or replace damaged or nonfunctional or dysfunctioning tissues</p> <p>Examples:</p> <ol style="list-style-type: none"> Diagnostic equipment Eradicate, ablate, or destroy tissue Enhance, augment, or substitute functioning of tissues or organs 	<p>Category 3: Clinical Improvement</p> <p>Examples:</p> <ol style="list-style-type: none"> Improve or stabilize clinical signs and symptoms of disease Reduce complications from surgery or drug therapy Disease modulation or modification 	<p>Category 4: Improved Clinical Outcomes</p> <p>Examples:</p> <ol style="list-style-type: none"> Disease progression; progression-free survival Reduce major cardiovascular events (MACE) Survival

(continued on pg. 12)...

Recommendations (continued from pg. 11)

A somewhat similar system is already in place in the [accelerated approval pathway](#), implemented under FDASIA. As an illustration, consider the claims language for two cancer drugs, [Ibrance](#) and [Keytruda](#), 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) for the drug. The only way approval could be revoked would be 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, 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. 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. Designations for orphan drug and qualified infectious disease product should remain.

Post-approval studies should be required only in well-defined situations

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. 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 post-approval studies, as occurred with Avastin for the treatment of breast cancer.

With respect to safety, observational postapproval studies to amass additional safety data are appropriate. However, studies to determine whether a new drug, for example, 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.

Make clear which decisions are the domain of the FDA (public health) and which are the domain of physicians, patients, and other members of 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 measured or analyzed in studies of the “average patient” because they can vary greatly from patient to patient. If sponsors seek 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.

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, and communicate clearly about, multiple measures of biological activity, which will allow more expeditious entrance into the medical armamentarium of new drugs that demonstrate safety and effectiveness. Postapproval studies performed by manufacturers (at their discretion), payers, hospital consortia, and medical societies will determine [\(continued on pg. 11\)](#)...

Recommendations (continued from pg. 12)

which drugs provide clinical benefit for patients, and accordingly, those drugs will be used preferentially. 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 lost sight of its proper role in the medical marketplace, but it has also been permitted to redefine its congressional mandate. The FDA is supposed to expeditiously judge whether new drugs can be labeled for safe use and whether substantial evidence exists that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling submitted for review by sponsors. However, the FDA 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 time and enormous cost of developing new drugs, which, in turn, drive drug prices upward.

However, the FDA is not solely at fault. 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) has 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. ■

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