United States Senate Committee on Homeland Security and Governmental Affairs

Title: Connecting Patients to New and Potential Life Saving Treatments

Description:

This hearing will focus on identifying possible barriers that prevent patients from accessing new and potentially lifesaving therapies, often in the face of terminal or debilitating conditions. We will hear from patients and experts about the steps Congress can take to reduce impediments and help connect willing patients and potential medical innovations.

Witness:

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Thank you for inviting me to participate in this hearing. I hope that my testimony proves useful to the Committee.

Introduction and Problem Statement

The Food and Drug Administration has been charged by Congress with a truly daunting responsibility with respect to drugs, biologics, and medical devices – to approve products that are safe and effective. 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."

Safety and effectiveness are the sole criteria that FDA is to use in determining which new products should be approved. In addition, Congress implied urgency to this function by using three key words – *promptly, efficiently, and timely* – and called for the FDA to be forward-looking – *promote health* – and not simply content with preserving the status quo.

However, we have seen progressive erosion of the safety and effectiveness cornerstone upon which FDA law has been built, and with that erosion, a loss of urgency to deliver safe and effective products to patients.

Safety and effectiveness are difficult enough to determine, and the FDA deserves our respect and admiration for the work that it performs along these lines. How much more

difficult and often impossible are other criteria and unrealistic expectations that have been wrongfully laid at FDA's doorstep?

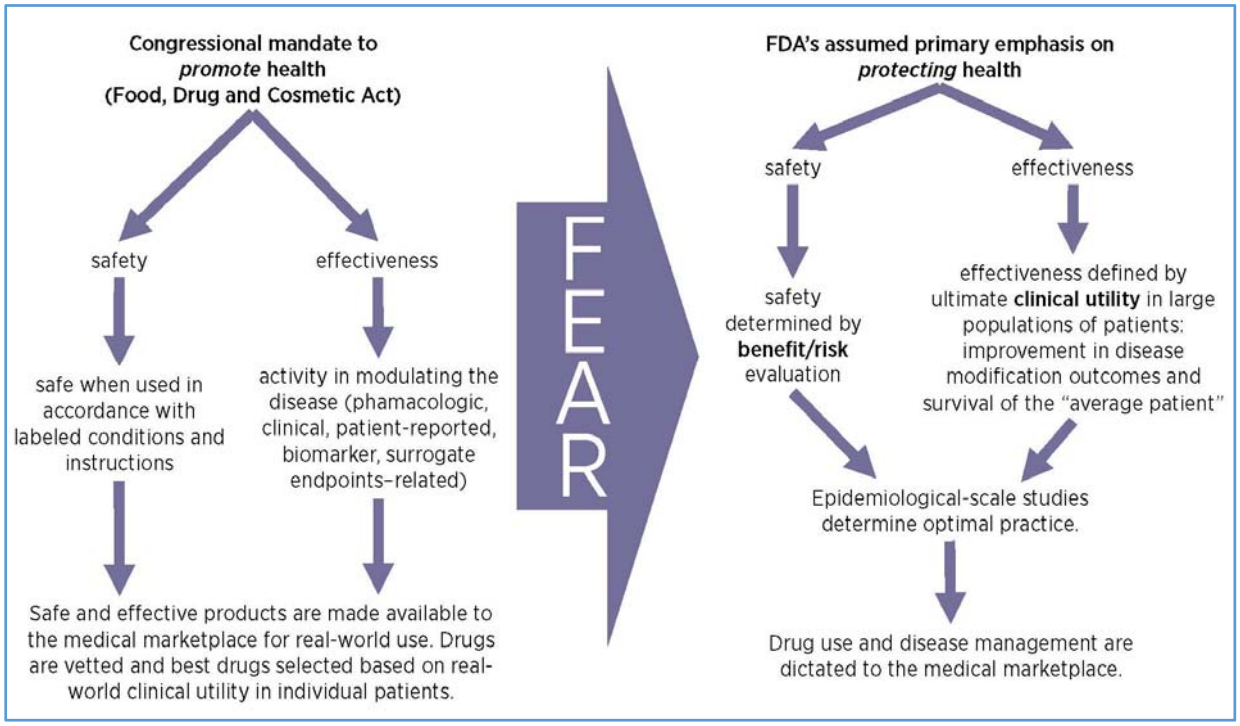
The expectation from certain areas of society is that the FDA completely defines the clinical utility, clinical outcomes, and benefit-risk of new drugs, and vets all potential side effects for all people in all situations, even effects resulting from uses that are not intended and are not in conformity 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.[1]

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 and of patients. Instead, over the last 20 years, the FDA has become markedly more restrictive concerning new drugs, particularly through 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.).

As Figure 1 depicts, fear has caused a shift in FDA posture from promoting health to protecting health. With this shift, the safety and effectiveness standard has been dramatically changed - safety no longer applies to the use of the drug according to conditions of use contained in the label and effectiveness no longer means substantial evidence of disease activity. In the fear-based paradigm, safety is determined by projected benefit-risk and effectiveness requires proof of clinical utility, outcomes and survival.

[1] 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.

Figure 1. Fear-based shift in emphasis to protect health and associated changes in the meaning of safety and effectiveness



The effect of the fear-based 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 (EBM), 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.[2] And so the trend has been for the FDA to become more and more restrictive, protracting its pre-approval processes and now frequently requiring that additional controlled trials be done *after* approval.[3]

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.[4] In a sense, the FDA has restated its mission from *promoting* health to *protecting* health—from permitting new safe and effective products that can advance health to demanding certainty that products will improve clinical outcomes and will not cause any harm. However, as drugs are small

[2] 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/.
[3] 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.

molecules designed to have an effect by binding to targets in the body, it is impossible to give assurance that no harm will ever occur.

Of course, protecting health is part of promoting health, however, the FDA has elevated "protecting" health as its main mission. Promoting and protecting health are two different postures – the latter looks to preserve that which currently exists while the former engenders optimism and belief in the advancement of scientific discoveries as a means of improving the health of Americans. Implicit in promoting health is an understanding that occasionally new products may not be found to be as desirable as we would like them to be, however, the only way to have genuine progress is to accept and deal with "bleeding edge" issues as we try to bring cutting-edge treatments and diagnostics to patients as soon as possible.

The Primacy of the Safety and Effectiveness Standard

The law reinforces the primacy of safety and effectiveness in FDA's decision-making as evidenced in the language of C.F.R. Title 21, Chapter 1, Subchapter D, Part 314, Subpart D, Section 314.125(b)(2)–(5), which lists permissible reasons to refuse an application. Specifying reasons for refusal implies that approval is the anticipated (or hoped-for) outcome:

> (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.

By listing the specific deficiencies for which approval can be withheld, as opposed to conditions that must be met for approval to be granted, the law clearly presumed approval to be the likely outcome. This makes sense because in order for review dossiers to be submitted, drugs (hereinafter inclusive of drugs, biologics, and medical devices) must first survive the low probability and roughly decade-long rigorous gauntlet of preclinical testing, early clinical development, and large late stage trials for sponsors to feel confident that the drugs meet the safety and effectiveness standard.

Safety and Effectiveness Does Not Mean Clinical Utility, Benefit-Risk, Survival, or Comparative Effectiveness

Notably absent in the law is any description of refusing an application on the basis of the FDA's predictions as to 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.[5] 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."[6] 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.

Benefit-risk is a private health decision to be made by doctors and patients when weighing whether to use drugs that are safe and effective (public health decision) – see Table 1. Interestingly, the criteria of safety and effectiveness are relative to that which the sponsor claims in its proposed labeling, not in the absolute. All drugs have side effects – the FDA's job is to label products appropriately so that they can be administered safely to patients for which they are intended. Benefit-risk is more of a labeling issue (relative to FDA's responsibility) than it is a basis for approval, yet, benefit-risk has seemingly supplanted safety and effectiveness as the operating approval standard.

[5] C.F.R. Title 21, Chapter 1, Subchapter D, Part 314, Subpart D, Section 314.125(b)(2)–(5).
[6] FDA, *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA V Implementation Plan*, February 2013, 2.

Table 1. Public Health Decisions (made by FDA) versus Private Health Decisions (made by patients and physicians)

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

The use of benefit-risk opens the door for FDA to make determinations regarding clinical utility (proof that the treatment positively modulates disease outcome) and clinical benefit (proof that the effect of the drug enhances the patients' lives). This completely changes the nature of pre-approval clinical trials because in order to provide substantial evidence of clinical utility and clinical benefit, even larger health outcomes trials and comparative effectiveness studies are necessitated in the premarket drug approval process. Although "benefit-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.[7] While clinical trials can readily show whether a drug is active in modulating disease parameters (lowering glucose levels, reducing pain, reducing tumor burden, etc.), however, even the largest trials cannot control for the myriad factors that affect ultimate outcomes (survival, reduction in end-organ complications, etc.). 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

[7] 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.

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. If required to better inform medical decision-making, 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.

Evidence Based Medicine Should Not Replace Private Health Decision-Making

Despite incessant pleas from doctors and patients for more safe and effective 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 to determine clinical utility, benefit, and health outcomes, pre-approval. 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.

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."

But the FDA is supposed to assure *safety and effectiveness of drugs*, not *life outcomes for patients*. A drug's proposed label indicates the effect it is purported to have; 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.

Certainly, studies of life outcomes can be invaluable to informed decision-making by physicians and payers. But there are many 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.

Moreover, the appropriate place to evaluate life outcomes is in the post-approval setting, by the medical marketplace. Trying to do so pre-approval, before a new drug has settled into practice, is not scientifically prudent. The myriad of real world factors that may modulate ultimate clinical benefit cannot be known or controlled in pre-approval studies, no matter the size, without informed data that become available only after a safe and effective drug has been in use for a period of time. Thus, the way that FDA currently approaches drug approval can actually mask clinical benefit. If clinical utility is used as the criteria for approval, many drugs that are safe and effective and could help patients will never see the light of day.

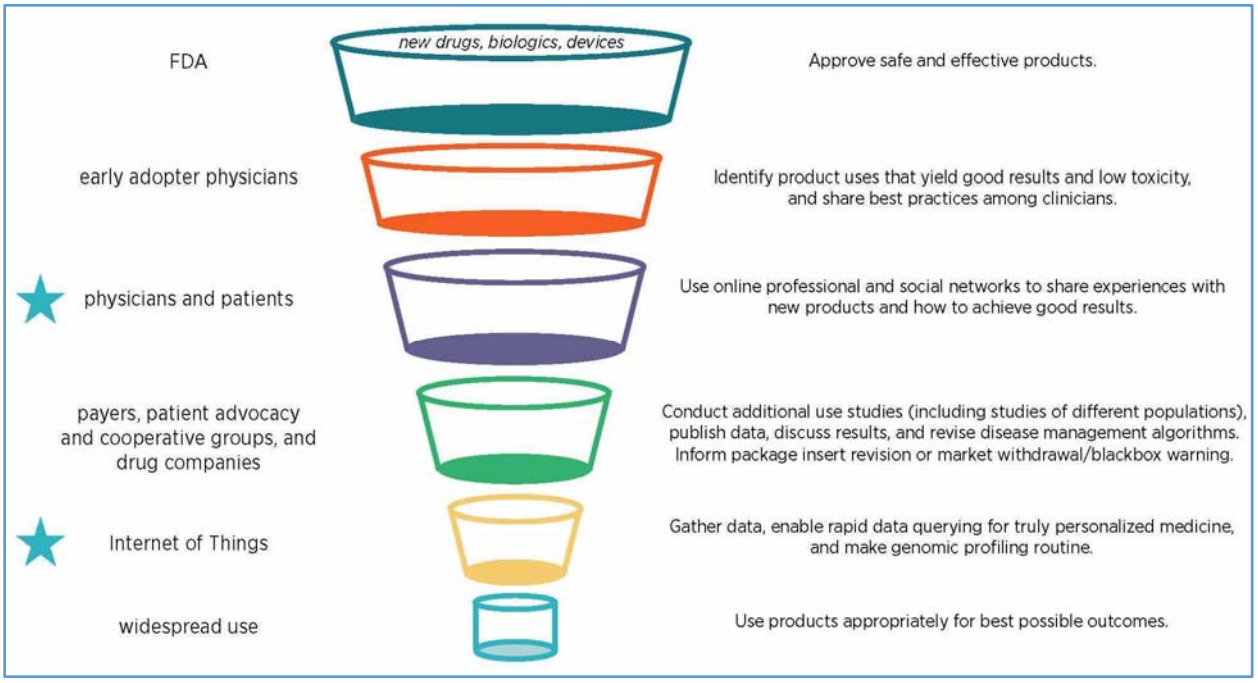
In fact, using life outcomes in clinical trials introduces a significant probability that a positive effect of the drug will be missed (false negative). The FDA cares more about reducing the chances of trials showing that there is a meaningful difference between treatment groups (new drug versus an alternative) when, in truth, there is no difference (false positive). In reality, patients (particularly patients with terminal illnesses) care more about trials missing a potential meaningful effect (false negative) - they would rather have more safe and effective products that could possibly help them than fewer products that are likely not inferior to other treatments.

How is Precision Medicine Best Practiced?

The other problem with the FDA's current approach is that it is directly contrary to the precision medicine movement. The FDA makes its determinations based on the responses of the average patient in clinical trials. While immediate- and near-term measures of effectiveness (reducing pain and tumor size, and increasing air movement in the lungs, for example) are appropriately evaluated by calculating average patient responses, clinical benefit is not appropriately assessed in this manner. Many patients may truly benefit from a drug, however, the benefit may not be seen in enough patients to pass the average patient hurdle. As long as the drug is safe and effective as per its labeled conditions of use, clinical benefit should be the domain of patients and doctors, not of the FDA.

In essence, the FDA, which should be the gatekeeper of safe and effective products that enter the medical armamentarium, has put itself in the position of judging which drugs are most beneficial. The funnel diagram in Figure 2 depicts the roles and responsibilities of medical marketplace constituents in the diffusion of new drugs and devices into practice. The law provides for the FDA to be at the top of the funnel and for the medical marketplace to decide from among the FDA-approved safe and effective products which are the most beneficial, therefore, which are used the most (bottom of the funnel). However, the FDA in demanding data from drug developers, pre-approval, to determine which drugs are most beneficial, is putting itself at the bottom of the funnel, as well.

Figure 2. The Medical Ecosystem & Marketplace – Appropriate Roles



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 safe and effective 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.

Patient Centered Development

There has been a great amount of discussion centered around the goal of bringing the voice of the patient into the development of new products. In the PDUFA VI meetings in October 2015, a proposal for advancing the science of patient input (Patient Focused Drug Development and Patient Reported Outcomes) was discussed. As summarized in the meeting minutes[8]:

> *FDA identified a need to bridge learnings from PDUFA V patient-focused drug development-type meetings to the development of methodologically sound fit-for-purpose tools to systematically collect key information about patients' experience including the burden of disease, and benefit as well as potential burden of therapy. To address this FDA proposed to use public workshops to*

[8] FDA-Industry PDUFA VI Reauthorization Meeting – Regulatory Decision Tools Subgroup October 7, 2015, 12:30am-2:30pm -

> *develop a series of guidances focusing on recommended approaches including collection of comprehensive patient-community input, impacts that are important to patients, and the measurement of those impacts. FDA noted that the capacity for increasing patient engagement and review work would require increased staffing.*

These efforts have been fruitless to date and are unlikely to yield substantive change. Existing laws, rules, and guidance documents provide for the use of patient-reported outcomes, for example, pain scales and activities of daily living. The best way to bring the voice of the patient into development and approval decisions is to not presume to be capable of ascertaining the voices of individual patients. These efforts are likely to end up being representative of the fictional average patient. Patient preferences are highly personal and diverse and as such, the assumption that the FDA can make these decisions on behalf of patients is unsound. These decisions are appropriately made by patients and their physicians as they decide on which (and whether) available safe and effective products will be employed to help them, not by the FDA.

It is imperative that the FDA get back to focusing on safety and effectiveness as the pre-approval standards. The flow of new innovative therapies that can advance health is dependent upon all players in the medical marketplace performing their role, starting with the FDA making safe and effective products available. Acknowledging that medicine is more of an art than a science and that the FDA is not the lone participant in the medical ecosystem responsible for advancing the health of Americans is the first step.

The Vicious Cycle that Erodes Safety and Effectiveness Standard

As former FDA Commissioner Alexander M. Schmidt said in 1974: "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." Castigation and public embarrassment of the FDA when unfortunate issues with approved products emerge as they are used in larger real world populations is the first step of the vicious cycle that has eroded the safety and effectiveness standard.

Congressional oversight has been exercised more as a “fire alarm” than as “police patrol,” in the words of McCubbins and Schwartz.[9] Congress has been deficient in “police patrol” oversight, that is, constant watchful vigilance to ensure that FDA laws are enacted dutifully. But, it has been quite aggressive in exercising “fire alarm” oversight in response to events like adverse reactions with medical products.

There have been many high-profile hearings on drugs including antidepressants, Vioxx, Rezulin, and Avandia. In all of these, the FDA is basically accused of inappropriately

[9] Congressional Oversight Overlooked: Police Patrols versus Fire Alarms. Mathew D. McCubbins and Thomas Schwartz. American Journal of Political Science. Vol. 28, No. 1 (Feb., 1984), pp. 165-179

approving products that are unsafe. Of course, the issues are not so cut and dry. This kind of knee-jerk oversight, which provides great, significantly damages the cause of medical innovation.

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. In 2007, a New England Journal of Medicine publication of a meta-analysis of 42 small clinical trials revealed an increased likelihood of significant cardiovascular toxicity in patients taking the drug, so the FDA restricted the drug's use in response to pointed criticism at a Congressional hearing. Here is what the FDA had to endure at a Senate 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?"[10]

Subsequently, the FDA removed the restrictions from the label when the drug was shown **not** to cause increased cardiovascular problems, following a re-analysis of a very large prospective study, rendering 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. Knee-jerk oversight triggered by a flawed analysis had severe unintended consequences.

Sadly, Dr. Robert Califf, nominated to be the new FDA Commissioner, was in full support of erroneously demanding larger and larger trials in the midst of the Avandia saga – As Matt Herper of *Forbes* writes:

> "In 2008, after Steven Nissen from the Cleveland Clinic had openly criticized Avandia, the GlaxoSmithKline diabetes drug, he proposed a new standard for studying diabetes medicines that would insist they be tested in clinical trials involving thousands of patients to see if they had any effect on heart attack rates. When Nissen mentioned the idea at an open public meeting, Califf was fast to back it."[11]

And, these sorts of unnecessarily large, expensive, and time-consuming studies have remained as the new standard – they were not walked-back when the case of Avandia was shown to be a false alarm. In December 2015, the FDA issued the following statement - "continued monitoring" of Avandia, Avandamet and Avandaryl had turned up "no new pertinent safety information" about the drug. 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

[10] Medscape. Avandia and FDA Both Subject of Severe Criticism at Congressional Hearing. May 11, 2010
[11] Forbes. Robert Califf Could Transform the FDA – The Right Way. September 16, 2015

from a peak of $3 billion before the controversy to $183 million in 2011, just before generics hit the market."

At the Senate HELP (Health Education Labor and Pensions) committee's confirmation hearing for Dr. Califf on November 15, 2015, he doubled down:

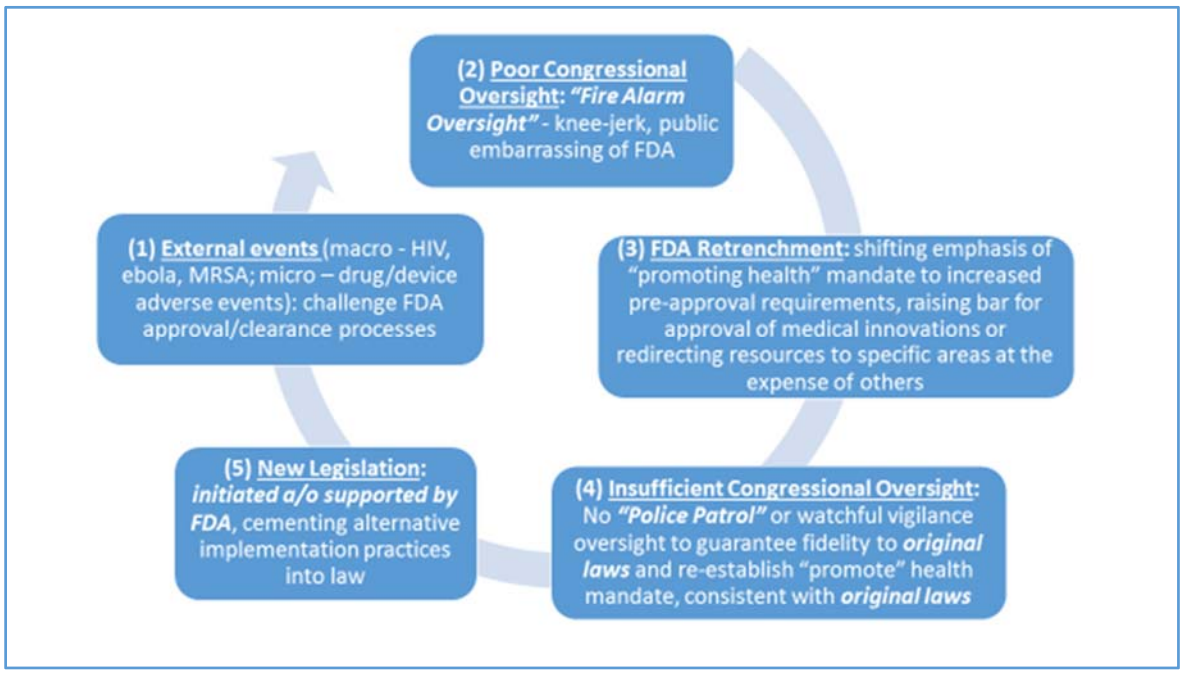
> Sr. Warren:" Do you agree with arguments to lower standards for FDA approval of drugs and devices?"
> D. Califf: "I have never been a proponent of lowering standards for anything,..I have been in favor of raising standards. In no case would I argue to lower the standard. I think I have been staunch in that regard."[12]

It is understandable that the FDA would recoil when it is attacked. The agency then protects itself from future attack by: (1) raising the bar for product approvals by moving away from the statutory criteria of safety and effectiveness and demanding proof of clinical utility, clinical outcomes and survival; (2) demanding larger and larger trials that cost tremendous amounts of time and money; (3) shifting its emphasis to pre-approval requirements versus a balance of pre-approval data and post-market controls and surveillance; and (4) preferentially approving products for niche diseases rather than those that affect millions of Americans. (See Figure 3, which depicts the Vicious Cycle.)

After FDA recoils in response to criticism and then issues new rules and guidance documents with alternative interpretations and implementations of the laws, Congress does not perform the appropriate police patrol oversight to re-direct the FDA back to its mandate, forcing the FDA to honor the letter and spirit of the laws. No, it does something worse – it actually passes more laws, for example, as part of each PDUFA (Prescription Drug User Fee Act) and MDUFA (Medical Device User Fee Act) reauthorization that takes place every five years, and in other legislation, like 21st Century Cures. This legislation, drafted in consultation with the FDA, then codifies the FDA's new positions taken in response to inappropriate fire alarm oversight.

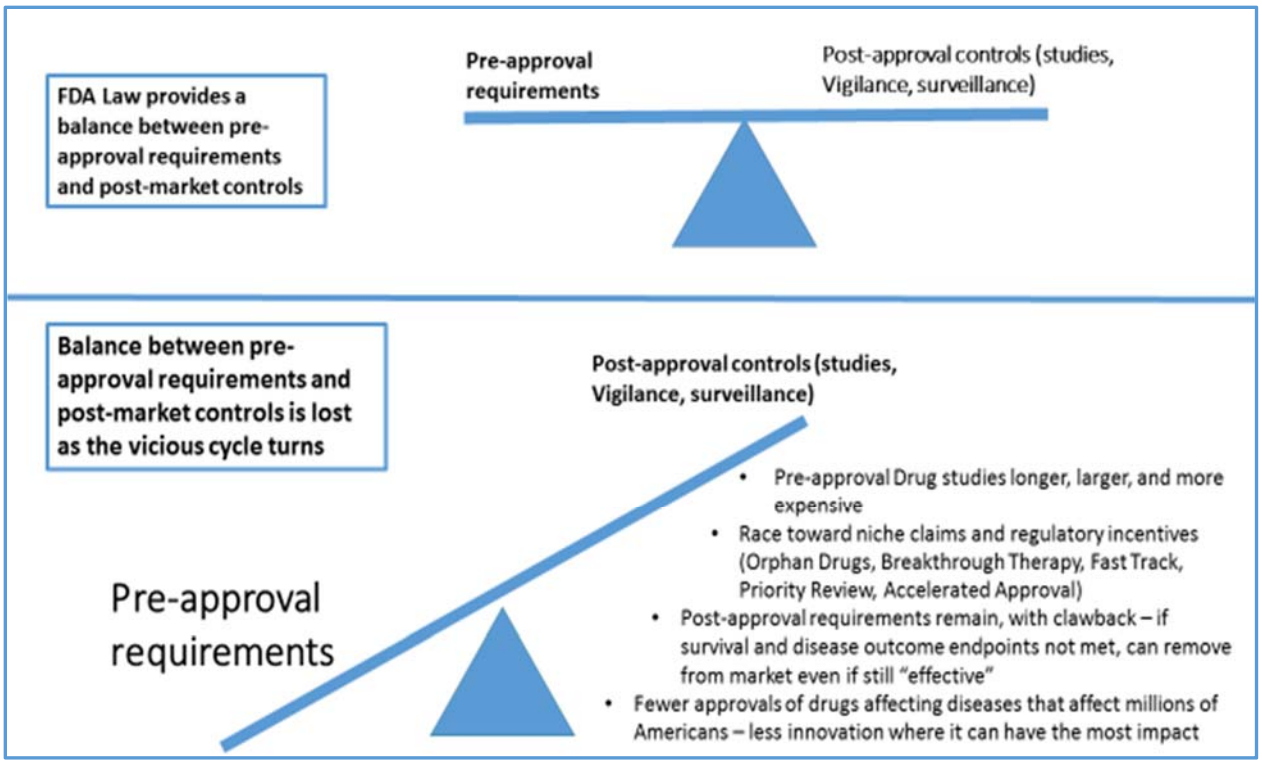
[12] BioPahrma Dive. Senators grilled Obama's nominee for FDA chief. Here's how he responded. November 18, 2015

Figure 3. The Vicious Cycle the Progressively Erodes the Safety & Effectiveness Standard



The vicious cycle starts over again the next time unfortunate adverse events occur with drugs and devices that are on the market, which invariably happens. This is how regulation kills medical innovation and hurts patients. With each turn of the vicious cycle, the safety and effectiveness standard is further eroded along with the nature and balance of pre-approval criteria and post-approval controls. Figure 4 demonstrates how the balance of pre-approval requirements and post-approval controls is shifted with each turn of the vicious cycle. It also demonstrates how the nature of the pre-approval requirements and post-approval controls are modulated.

Figure 4. Shift in balance and nature of pre-approval requirements and post-approval controls as the vicious cycle erodes the safety and effectiveness standard



Rise of Specialty and Orphan Drugs in Lieu of Drugs Treating Diseases with Large Populations of Patients

A direct outcome of this vicious cycle is the rise of specialty pharmaceutical products intended for small populations of patients. In 2014, the FDA approved 41 new drugs – more than in any year since 1996, according to the agency's numbers. In 2015, 45 novel new drugs were approved. Many have cited these statistics as proof that the agency is performing well, consistent with its mission since the 2014 total was more than double that of 2007. However, 40% and 47% of the drugs that were approved in 2014 and 2015, respectively, were for niche orphan diseases, that is, conditions affecting less than 200,000 patients per year. There were 467 requests for orphan designation last year by the pharmaceutical industry (~35% increase from 2013), and 293 drugs were granted orphan status by the FDA (13% increase).

Given these statistics, it becomes obvious that the industry's focus on niche specialty drugs as opposed to drugs for diseases that affect millions of Americans is driven by the erosion of the FDA's safety and effectiveness standard for approvals.

The FDA, following public ridicule in oversight hearings of drugs for diabetes and arthritis, has imposed new standards for approval – not only must drugs for diseases that affect millions of Americans (diabetes, cardiovascular disease, COPD, obesity, etc.)

prove clinical utility (as opposed to disease activity as embodied in the effectiveness standard), they must be studied in huge trials and either show an improvement in – or no deleterious impact on – survival and major adverse cardiac events. And, even at that, the FDA requires large and expensive post-approval studies to confirm the findings.

The FDA has imposed a de facto "better than the Beatles" standard, as well; basically, if the drugs are not shown to be more effective or safer than drugs already on the market (in large trials using the "average patient standard") the FDA typically denies their approval. [This is very unfortunate because often, many patients experience benefit of a drug on an individual basis and the effect is lost when patient responses are averaged over the entire study population.] So, companies have increasingly foregone the development of drugs for these diseases and focused on rare diseases and conditions for which no other therapies exist. These qualify for Orphan Drug, Fast Track, BTD, Expedited Review, and Accelerated Approval, which provide substantial regulatory incentives (reduced review times, smaller trials, etc.).[13]

> *…Add to that the benefit of lower R&D costs. Derek Fetzer, director, global strategic analytics/global strategic marketing & market access, at Janssen Pharmaceutical Services, says that this made it worthwhile for a big firm like J&J to make a move into the specialty arena: "Improving on the many good drugs on the market is a significant, technical challenge," he observes. "This is because demonstrating smaller, incremental benefits actually requires more patients in a clinical study, from a statistical point of view, and thus is more costly."*
>
> *Compared to PCP-focused candidates (drugs for use by primary care physicians), specialty medicine clinical development can be not only less expensive but offer a nearer-term opportunity for cashing-in on an investment. Specialty medicine candidates typically are vetted by big pharma along the dimensions of demonstrating substantial innovation, where R&D efforts can require fewer patients and significant differences can be demonstrated over a shorter period of time.*
>
> *There are regulatory rewards, too. The most prominent "X-factor" in new drugs—the FDA—displays more love toward products that aspire to occupy salient treatment voids as opposed to those gaining incremental yardage vs. existing therapy. Indeed, this is an essential element of FDA's charter. "One central factor FDA takes into account in determining the speed of review of a new product application is whether it addresses an unmet medical need, hence potentially translating into shorter time to market," says Wayne Pines, former FDA associate commissioner, who is now president of regulatory services and healthcare for APCO Worldwide. "A usual review is 10 months and a fast-track or priority review is six months or less."*

[13] Specialty Pharma: Niches to Riches. Medical Marketing and Media, March 1, 2012.

And, these specialty products are very expensive for two reasons – the number of patients for which they can be used is small, and there is literally no competition, meaning no other drugs approved in these settings.

Getting the FDA Back to Safety and Effectiveness

Unfortunately, better oversight alone cannot make up for the problems that have been caused by many turns of the vicious cycle. Therefore, legislation is necessary to essentially re-set the FDA back to the foundations that were established prior to the user fee era. This includes:

1. Restatement of **promoting health** as the FDA's principal function with respect to new products. The law states the following as FDA's mission - "to promote health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion." The law is actually biased toward embracing medical innovation by assuming that new drugs that undergo the drug development gauntlet would be approved, **unless** the drugs (or applications) had certain deficiencies. This attitude and inclination is not embodied in many FDA regulations and guidance documents, as well as in new sections of the law that have been passed as part of reauthorization legislation. The law also provides for a balance between pre-approval hurdles and post-approval controls and makes clear that approval should not be denied in cases where questions about a drug or device could be answered in the post-approval setting via post-market controls (studies, vigilance, and surveillance).
2. Restatement of **safety and effectiveness** as the only requisite standards for approval of new products. (For devices, reaffirmation of reasonable assurance of safety and effectiveness, and least burdensome approach is needed.) Legislation needs to explicitly state that effectiveness is to be evaluated by the FDA in accordance with the labeling proposed by the sponsor and that the FDA is not to impose standards requiring demonstration of clinical utility for approval. The FDA can and should limit the claims based on the data – if there are no clinical benefit data in the application, then clinical benefit should not be claimed. Likewise, legislation that explicitly lists acceptable measures of effectiveness that can support approval – pharmacodynamics effects on disease parameters, clinical signs and symptoms, biomarkers, surrogate endpoints, patient-reported data, comparative effectiveness, clinical outcomes, and survival. A strong caveat that comparative effectiveness, survival, and disease outcomes are not needed to demonstrate effectiveness, but are needed to obtain claims that include these parameters is needed. The legislation should also state the approved label will contain the measures used to determine effectiveness and claims will be limited to the specific findings.
3. Congress can greatly help the FDA by providing for categories of approval according to the nature of the data used to provide substantial evidence of effectiveness, and if sponsors so desire to obtain additional, 'higher order' categories (for example, survival and disease outcomes), supplemental approval

applications can be submitted. Such a system might lay out four categories of approval, as in the following example:

> 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, CEA – carcinoembryonic antigen, CD4/CD8 ratio, PSA – prostate specific antigen, INR – blood clotting, 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, pre-mature ventricular contractions), etc.
>
> Category 3. **Disease Modification**—reduction in flares of diarrhea, reduced joint space narrowing; reduction in MS relapses; reduction in the use of other medications (steroids); reduction in development of deep vein thrombosis or pulmonary embolism; reduction in sickle cell crises; etc.
>
> Category 4. **Clinical Utility/Outcomes**—improvement in survival, reduction on major cardiac events (myocardial infarction, heart failure, re-hospitalization), etc.

4. Provisions for Breakthrough Therapy Designation, Accelerated Approval, Fast Track, Priority Review and Accelerated Approval should be rescinded –with enforcement of the effectiveness standard defined in #2 above and with the FDA meeting its review time frames these programs will no longer be needed. [Orphan Drug designation and Qualified Infectious Disease Product should remain.]
5. Post-approval studies should be limited to amassing greater safety databases to inform labeling. Studies performed to generate evidence for higher order effectiveness claims shall not result in market withdrawal if higher order effectiveness objectives are not met. This is in contrast to the current regulations, which allow for rescinding product approval if drugs approved on the basis of surrogate endpoints (Accelerated Approval) are not shown to have improved disease outcomes and survival in post-approval studies.
6. Personalized medicine in the real world should be fostered, as well. Legislation should make clear which decisions are the domain of the FDA (public health) and those that are the domain of physicians, patients, and other members of the medical marketplace ecosystem (private health). FDA is responsible for safety and effectiveness. Clinical utility and clinical benefit often cannot be easily measured or analyzed in “average patient studies” because these can vary greatly from patient to patient. If sponsors seek claims that communicate clinical utility and clinical benefit, then, the sponsor 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. Ideally, to further foster personalized medicine, the data from clinical trials should be made available to practicing physicians

who would then be able to query the databases to obtain knowledge of the effects of the drugs on patients given certain demographic and genetic profiles; this will aid physicians in their private health decisions.

Another recommendation is for Congress to refrain from using hearings as a venue to publicly embarrass and humiliate the FDA when products that have been approved are shown to have undesirable effects and toxicities when used in the real world in larger numbers of patients. This initiates the vicious cycle that stifles medical innovation which was previously illustrated in Figure 3.

It also sets an expectation in the eyes of the public for the FDA to be perfect when it comes to the review and approval of new products. We should not be conditioned to expect perfection, rather, we should be assured that proper mechanisms are in place to appropriately judge the safety and effectiveness of new products and to track them and rapidly report any issues that might emerge after approval. The FDA should then act, appropriately, either with revised labeling or other actions, including removal from the market in extreme settings. Congress would do well to reinforce to the public that the FDA is just one member of the medical ecosystem – physicians, medical societies, hospitals, cooperative research groups, drug companies, and clinical researchers have an important responsibility to disseminate information quickly and to educate medical professionals and the public. Placing blame at the door of the FDA is neither accurate nor conducive to fostering medical innovation.

Conclusion

As Richard M. Cooper, Food and Drug Administration (FDA) Chief Counsel, said in 1978, "The perception that agencies are out of control arises from the fact that in being called on to make fundamental value judgments they have moved outside their accustomed sphere of activity, outside their expertise, and outside the established system of controls. This perturbation of the regulatory process will not be corrected until the regulatory agencies are relieved of the necessity of making judgments they are not equipped to make." The FDA was never intended, and is not equipped, to make value decisions for individual patients. These are private health decisions. Congress charged the FDA with a public health mandate to approve drugs that are safe effective for physicians to use in the care of their patients, on an individual basis.

The key to reducing the amount of time required for potentially life-saving and life-enhancing treatments to reach patients is to restore the FDA to its proper role in the medical marketplace, that is, to the role of gatekeeper with regard to the entry of safe and effective drugs into the medical armamentarium. It is in the medical ecosystem that the diffusion of drugs into practice takes place. The medical marketplace constituents (early adopters, medical consortia and societies, hospitals, doctors, payers, and patients) decide which safe and effective products are the most beneficial and which should be prescribed in widespread fashion. This occurs after using the products in the real world for a period of time; much more is learned about the clinical utility and potential benefits in day to day use than is possible during large clinical trials of highly selected patient populations.

Attempts to approve only those drugs that have shown clinical utility in massive randomized clinical trials prior to approval serve to deprive patients and physicians of safe and effective products that could ultimately be enormously beneficial to them. This also runs counter to medical practice, which is as much art as science and requires direct first-hand experience with drugs to determine which are most appropriate in the real world on an individual basis. Another unintended consequence is that drug developers will focus on developing drugs for niche indications that serve small populations where clinical benefit is obvious because no other treatments are available. This reduces investment and research and development in products aimed at diseases affecting large populations of patients.

Determining safety and effectiveness is a daunting responsibility that should not be encumbered with unrealistic expectations – the FDA cannot make perfect public policy decisions. Neither is it possible for the FDA to make private health decisions that are based on benefit-risk for individual patients. FDA's role is to provide information in the labeling – the parameters within which drugs can be administered safely to achieve the approved effects – that doctors and patients can use in their decision-making.

The FDA is not in it alone despite having been made to feel that it, indeed, is solely responsible for health and well-being of the American public. In order to be effective, the FDA needs the support, understanding, and confidence of the American public in fulfilling their crucial and proper role.

Attachments:

The Proper Role of the FDA in the 21st Century – February 2016

FDA must focus on drug safety and effectiveness, not patients' life outcomes – The Hill, February 19, 2016

Meet FDA critic Joseph Gulfo, the Antonin Scalia of the life sciences – Boston Business Journal, February 18, 2016

COMMENTARY: Return FDA to its proper role – Courier Post, February 7, 2016

Appropriate oversight is needed to change FDA behaviors, not more laws – The Hill, December 22, 2015

MI3 Alert - Congressional Oversight of the FDA – December 1, 2015

FDA 2014 Approvals – The Message Behind the Numbers – The Hill, January 8, 2015

GULFO: "Right to Try" just another bandage on a chronic wound – Washington Times, July 11, 2014