General Description of Issue

Oversight of the Executive Branch is a main duty of Congress that is implied, rather than an enumerated power – it was seen in the Federalist Papers (48, 49, and 51) as an inherent power of representative assemblies, which enacted public law. Oversight also derives from the many, varied express powers of the Congress in the Constitution - it is implied in the legislature's authority, among other powers and duties, to appropriate funds, enact laws, and impeach and remove from office the President, Vice President, and other civil officers. Congress could not reasonably or responsibly exercise these powers without knowing what the executive was doing; how programs were being administered, by whom, and at what cost; and whether officials were obeying the law and complying with legislative intent. However, as former House Speaker Tip O'Neill once exclaimed, “Members like to create and legislate, but we have shied from both word and deed of oversight.” As former Speaker Newt Gingrich said, “This is the city [Washington, DC] which spends almost all of its energy trying to make the right decisions and almost none of its energy focusing on how to improve implementing the right decisions. And without implementation, the best ideas in the world simply don't occur.” Congress certainly expends great effort passing laws that have the goal of enhancing medical innovation, for example PDUFA (Prescription Drug User Fee Act) and MDUFA (Medical Device User Fee Act) reauthorization. The question is whether better Congressional oversight would result in a greater number of more profound medical innovations reaching patients more quickly.

Purposes To Do

Congressional oversight of the FDA could be a very powerful force to ensure that the letters and spirits of FDA laws are enacted in a manner that truly enhances medical innovation. Congress has at its disposal many opportunities to conduct this oversight, including: (continued on pg. 2)...

Success in Achieving Objective: +3

Potential Positive Impact on Innovation

The potential positive impact on medical innovation that would follow effective Congressional oversight is enormous. Oversight on just a handful of policies could have a huge impact: (continued on pg. 2)...

Positive Impact on Innovation: +3

Potential Negative Impact on Innovation

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 that comes from hearings in response to events, for example adverse (continued on pg. 6)...

Negative Impact on Innovation: -4

\[\text{Mi}^3 \text{ Score } = -1\]

If poor oversight were eliminated and proper oversight were implemented, a substantial positive impact on medical innovation is likely

Recommendations

As Walter Oleszek of the Congressional Research Service states in Congressional Oversight: An Overview:

Conessional oversight ideally involves the continuous review by the House and Senate, especially through their committee structures, of how effectively and efficiently the executive branch is carrying out legislative mandates. The “continuous watchfulness” precept—an obligation statutorily assigned to the standing committees by the Legislative Reorganization Act of 1946—implied that Congress would henceforth participate actively in administrative decision-making, in line (continued on pg. 10)...

Unintended Consequences

Inaccurate Performance Reports:

As mentioned above, the FDA is required to make reports to Congress on review time performance under PDUFA [Federal Food, Drug, & Cosmetic Act (FD&C) (continued on pg. 3)...

Emergence of Unintended Consequences: -3

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

1. **Hearings and investigations** - hearings, in particular, focus generally on the efficiency and effectiveness of federal agencies and programs. They are also conducted in response to issues that arise as a perceived consequence of agency action or inaction.

2. **Authorizing process** - the regular reauthorization process of laws focuses great attention to spending and whether the spending authorized by Congress results in the desired effects. For example, PDUFA and MDUFA require reauthorization every 5 years.

3. **Appropriations** - as James Madison stated, “The power over the purse may, in fact, be regarded as the most complete and effectual weapon with which any constitution can arm the immediate representatives of the people, for obtaining a redress of every grievance, and for carrying into effect every just and salutary measure.”

4. **Inspectors General** - conduct investigations and audits of agencies to improve efficiency, end waste and fraud, discourage mismanagement, and strengthen the effectiveness and economy of agency operations.

5. **Government Accountability Office** - the office submits reports to Congress annually, describing ways to root out waste and mismanagement in executive branch programs and to promote program performance.

6. **Reporting Requirements** - numerous laws require executive agencies to submit reports periodically, and as required by specific events or certain conditions. For example, the FDA is required to provide Congress with yearly reports of review performance under PDUFA and MDUFA.

7. **Senate Confirmation Process** - through public questioning and review of credentials of individuals nominated by the President to lead agencies, Congress can bring to light issues in the implementation of the law by the agencies.

8. **Casework** - activities by members pursuant to issues raised by individual constituents.

9. **Informal** - member and staff contacts with agency personnel.

To the extent that many portions of FDA laws are designed to promote health through medical innovation, Congress has the mandate and multiple means at its disposal to conduct appropriate and effective oversight to ensure that the provisions and programs are being enacted as intended and achieving the desired goals.

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

1. If **PDUFA and MDUFA review time goals were enforced**, drug approval times would be cut in half and new devices would reach patients much more quickly:
   a. In 2013, the FDA’s median approval time for drugs was 304 days – this means that review times exceed the PDUFA goal of 10 months for 50% of applications.
   b. In the first half of 2015, the average review time for a Pre-Market Approval Application (PMA) was 17.1 months (MDUFA goal 180 days) and Humanitarian Device Exemption (HDE) took 16.7 months (MDUFA goal 75 days). In 2014, the average review time for a 510(k) was 6 months (MDUFA goal 90 days), and a company submitting a 510(k) had just a 22% chance of getting it cleared within the 3 month target, and a 61% chance of getting it cleared within 6 months.
   c. Moreover, many programs that were implemented to expedite the review and approval of certain classes of novel products (rare and diseases for which there are no other therapies or significant unmet medical needs) would not be needed if the FDA met the target review times in PDUFA and MDUFA.

2. If Congress conducted proper oversight of the FDA, the **safety and effectiveness standards** for drug and device approval, as well as the reasonable assurance of safety and effectiveness standard and the least burdensome approach for medical devices would be appropriately followed. The FDA has moved away from approving drugs and biologics that are - as stated in the regulations - “safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling” on the basis of clinical trials that demonstrate activity in important disease parameters (clinical activity in ameliorating disease signs and symptoms, surrogate endpoints, and biomarker responses) in favor of endpoints like Major Adverse Cardiac Events (MACE) and survival. Moreover, in practice, the FDA has replaced the safety and effectiveness standard with “clinical benefit,” going so far as to tell sponsors which indications for use the FDA deems appropriate as opposed to reviewing clinical studies and data for the claims that sponsors endeavor to develop. This is not how the laws are written or intended. The standards for FDA approval have become more onerous resulting in longer and larger clinical trials, which prevent and delay important medicines and devices from reaching patients. (continued on pg. 3)...
<table>
<thead>
<tr>
<th>Potential Positive Impact on Innovation (continued from pg. 2)</th>
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<td>The law is very clear regarding the evidentiary standard for drug approval – “the term “substantial evidence” means “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” (FD&amp;C 505 – 21USC 355(d)?).” Substantial evidence does not refer to clinical benefit or survival or other disease outcomes, rather to conducting adequate studies from which to conclude that the purported effects are real and reliable.</td>
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<td>a. Indeed, if Congress exercised proper oversight to enforce review times and standards of safety and effectiveness, it would not have been necessary for them to pass more laws ushering-in the rapidly-expanding series of regulatory incentives for niche carve-out areas of “high unmet medical need” with such programs as Fast Track, Priority Review, Breakthrough Therapy Designation (BTD), and Qualified Infectious Disease Products (QIDP), pediatric exclusivity, and Rare Pediatric and Tropical Diseases Priority Review vouchers.</td>
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<td>3. If Congress conducted proper oversight, issues that arise in the review of new products would be properly adjudicated. Sponsors have the ability to challenge FDA reviewers through the FDA Ombudsman; however, the Ombudsman does not report to the commissioner, rather, the Center for Drugs Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDHR) each possess a separate ombudsman who reports to the center directors. If the ombudsman reported to the commissioner and made regular reports to Congress as part of oversight, the FDA would be less likely to change approval standards, ignore prior agreements with companies on the clinical studies required to demonstrate safety and effectiveness, and would be less likely to request information during reviews that extends the review time limit, all of which would increase the certainty, consistency, and timeliness of new product reviews, which are the intended effects of the laws.</td>
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<td>4. If Congress conducted proper oversight of the Advisory Committee process for new drugs, biologics, and devices, experts in the medical fields of study would be required to review new products. However, often, the FDA does not include several or any physicians who treat the disease under review. “For the purpose of providing expert scientific advice and recommendations to the Secretary (secretary of HHS – Health and Human Services) regarding a clinical investigation of a drug or the approval for marketing of a drug under section FD&amp;C 505 or section 351 of the Public Health Service Act, the Secretary shall establish panels of experts or use panels of experts...” The statute goes on to say, “...members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs,” and “...two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.” If experts were included on panels routinely, the importance of findings from clinical studies would be better appreciated, labeling recommendations would be more clinically relevant, and more drugs and devices would reach patients sooner.</td>
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<th>Unintended Consequences (continued from pg. 1)</th>
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<td>Section 736B. – 21 USC 379h-2) and MDUFA (FD&amp;C Section 738A. – 21 USC 379j-1). However, the reports are very difficult to interpret and have little grounding in the real world metrics that Congress requested. As former FDA reviewer Henry Miller pointed out:</td>
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<td>I was struck by the dissonance between a statement by (FDA Commissioner) Dr. Hamburg several years ago and the FDA’s performance where it counts—getting new medicines to patients. She bragged that “[p]reliminary results of reviews completed during FY 2010 indicate that FDA has the potential to meet or exceed almost all (11 of 12) FY 2010 review performance goals.” But 2010 was the worst year for drug approvals in a quarter century. This kind of disconnect is typical of not only FDA but of other federal agencies: They create easily-met performance milestones that may have little relationship to the agency’s actual mission. Invoking the old medical cliché, the operation was a success but the patient died.</td>
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<td>Take for example the way review time is counted. The regulations call for non-priority NDA’s (New Drug Approvals) to be conducted within 10 months. However, in reports to Congress, the FDA counts review time in “review days” not calendar days, whereby the FDA stops and starts the review clock at its discretion, typically requesting that sponsors answer questions that emerge in the review of new products by submitting PMA, NDA, and BLA amendments, which then extend the review period. This has the effect of increasing the percent of applications reviewed within target dates defined in PDUFA and (continued on pg. 4)...</td>
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Untended Consequences (continued from pg. 3)

MDUFA and reported by the FDA to Congress, making performance appear to be within (or close to) review period goals, even when, on a calendar basis, review times far exceed the statutory targets. Also note that the FDA reports performance in median review times; average review times are calculated by outside analysts.

The laws that Congress passed do not say that reviews should be conducted within a certain number of review days, rather they state periods of time (months for drugs and biologics and days – not “review days” - for devices). Moreover, the FDA reports its performance in median review days, not average review days. Apparently, Congress did request that the FDA report the average number of days, but the average review time has not been adopted by the FDA as the primary measure. And, the FDA does not report average review time performance on a rolling ongoing basis:

As stated in the 2014 MDUFA Performance Report: FDA committed to report the average total time to final decision once decisions were made for 99 percent of the PMA cohort and 95 percent of the 510(k) cohort. FDA has made decisions on 98 percent of the FY 2013 510(k) cohort and the average total time to decision is 126 total days. Currently, FDA has made decisions on 73 percent of the FY 2013 PMA cohort, 16 percent of the FY 2014 PMA cohort, and 58 percent of the FY 2014 510(k) cohort and cannot yet report average review times. Once the required percentage of each cohort has received a decision, FDA will report the average time to final decision in future reports.

Even when Congress performs some degree of oversight – demanding performance reports, for example – it does not insist on receiving a clear accounting of performance based on discrete measures that it desires to review. This has significant unintended consequences – poor oversight gives the appearance that the FDA is performing well in its mission to promote health, when it is not. Absence of transparent information is one thing; accepting misleading information is quite another. And, Americans are not served well by either. As Walter J. Oleszek of the Congressional Research Service explains:

Woodrow Wilson, in his 1885 classic titled Congressional Government, declared that Congress informing function “should be preferred even to its legislative [lawmaking] function.” He explained: Unless Congress have and use every means of acquainting itself with the acts and dispositions of the administrative agents of government, the country must be helpless to learn how it is being served; and unless Congress both scrutinize these things and sift them by every form of discussion, the country must remain in embarrassing, crippling ignorance of the very affairs which it is most important it should understand and direct.

Redundant and Conflicting Laws:

Because the first inclination of lawmakers is to pass laws rather than to perform oversight, many new laws are redundant with laws that have been passed previously, and conflict with prior laws:

1. Consider FDASIA (Food and Drug Administration Safety and Innovation Act) that reauthorized PDUFA in 2012. One of the key provisions of this law was Breakthrough Therapy Designation (BTD), a program to expedite the review and approval of a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness. Looking at the Guidance Document on Expedited Programs for Serious Conditions – Drugs and Biologics, one is hard pressed to see how BTD added to the other programs that were already in the law to accomplish this, including Fast Track [included in the 1997 PDUFA reauthorization called the Food and Drug Administration Modernization Act (FDAMA) of 1997], Priority Review (included in the 1992 Prescription Drug User Fee Act), and Accelerated Approval (FDASIA 2012). Moreover, many products have been given several of these designations, and Orphan Drug Designation, as well (see Esbriet – perfenidone, Opdivo – nivolumab, and Xalkori – certitinib); in fact, 56% of novel products approved in 2012 qualified for multiple expedited programs, thereby demonstrating the redundancy and lack of need of BTD. These programs are very redundant, both in substance and spirit. If Congress knew the contents of the law by performing proper oversight, these laws would not have been passed. Deficiencies in the implementation of Priority Review, for example, could easily have been addressed in oversight, rather than in two major laws that ushered-in Fast Track and Accelerated Approval. And, if the law needed to be tweaked subsequent to the acknowledgement of deficiencies in the original statute that came to light during actual implementation, subtle amendments to Priority Review could have sufficed. (continued on pg. 5)...
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Unintended Consequences (continued from pg. 4)

Comparison of FDA’s Expedited Programs for Serious Conditions

<table>
<thead>
<tr>
<th>Nature of program</th>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
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<tbody>
<tr>
<td>Reference</td>
<td>● Section 506(b) of the FD&amp;C Act, as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)</td>
<td>● Section 506(a) of the FD&amp;C Act, as added by section 902 of FDASIA</td>
<td>● 21 CFR part 314, subpart H</td>
<td>● Prescription Drug User Fee Act of 1992</td>
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<td>Qualifying criteria</td>
<td>● A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR ● A drug that has been designated as a qualified infectious disease product</td>
<td>● A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</td>
<td>● A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)</td>
<td>● An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR ● Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A OR ● An application for a drug that has been designated as a qualified infectious disease product OR ● Any application or supplement for a drug submitted with a priority review voucher</td>
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### Potential Negative Impact on Innovation (continued from pg. 1)

Reactions with medical products. Recently, calls for Congressional hearings on surgical meshes, intrauterine devices for birth control, and endoscopic equipment that spread antibiotic-resistant infection have been made. 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 approving products that are unsafe. Of course, the issues are not so cut and dry. However, this kind of oversight greatly damages the cause of medical innovation:

As early as 1974, FDA Commissioner Alexander M. Schmidt said: “In all of FDA’s history, I am unable to find a single instance where a congressional committee investigated the failure of FDA to approve a new drug. But the number of 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.” In other words, no problem as long as the victims are invisible.

Faced with Congressional oversight that seeks to blame the FDA when toxicities emerge from the use of new products that have been approved, the FDA does three things: (1) it retrenches and shifts its emphasis to a significantly disproportionate reliance on pre-approval requirements, as opposed to postmarket controls, thereby adopting a “protect health” posture at the expense of its “promote health” mandate, as defined in the law; (2) it re-states statutorily-defined approval standards for 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) to unequivocal clinical utility and clinical benefit (as defined by the FDA, not sponsors), as well as to survival and disease outcomes; and (3) it seeks to limit the populations for which new drugs are approved to treat, hence, the unprecedented rise in orphan drug designations – two hundred ninety-one in 2014 - and approvals for niche specialty claims in recent times. 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 severely hinder the development of new products that may be of great help to patients.

The case of Avandia, a diabetes medication, is particularly illustrative: (1) a New England Journal of Medicine publication of a pooled study meta-analysis revealed an increased likelihood of significant cardiovascular toxicity in patients taking the drug; (2) the FDA restricted the drug’s use in response to pointed criticism at a Congressional hearing; and (3) the FDA removed the restrictions from the label when the drug was later shown not to cause increased cardiovascular problems, following a re-analysis of a very large study. 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.

A study led by Dr. Steven Nissen of the Cleveland Clinic linked Avandia to a 43% increased risk of having a heart attack and a 64% increased risk of death due to heart disease. The findings, based on data pooled from 42 small clinical trials, were published in the prestigious New England Journal of Medicine.

Those results prompted some experts to question how well the FDA was monitoring the safety of prescription drugs. Just a few years earlier, the federal agency withdrew its approval of the painkiller Vioxx after evidence emerged that it doubled the risk of heart attacks and strokes. When the critique of Avandia emerged, three major congressional committees announced their intention to investigate.

The FDA responded by adding warning labels to Avandia.

A new analysis this year by an FDA advisory panel suggested the initial concerns about Avandia were overblown. Members of the panel pointed to design flaws in Nissen’s study and said their evaluation found no evidence that the drug made patients more vulnerable to heart attacks or other heart problems.

The initial “signal of increased risk of heart attacks” reported by Nisen in 2007 has not been confirmed, the FDA said in the statement.

As a result, the FDA will no longer require doctors to limit Avandia prescriptions to certain patients. Its new label will likely state that anyone with Type 2 diabetes can use the drug in combination with diet and exercise to control their blood sugar, the agency said.

**Attacks on the FDA at Congressional hearings** due to the Avandia meta-analysis data, that were shown to be erroneous later, were vicious:

The report, by Sens Max Baucus (D-MT) and Charles Grassley (R-IA), concluded that there are “serious health risks associated with Avandia.” It also criticized the structure of the FDA, particularly the fact that those who make decisions about drug approvals are the same experts who must later oversee drug safety. (continued on pg. 7)
Introducing the Congressional hearing, subcommittee chair Rep Rosa DeLauro (D-CT) said: “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?”

What does the FDA do when it is attacked in this way – as stated above, it runs for cover and ratchets-up the pre-approval requirements for drugs that are used chronically in large numbers of patients and preferentially approves drugs for niche diseases and conditions. Of great concern is that the President’s nominee for FDA Commissioner, Dr. Robert Califf, is a fervent supporter of onerous approval requirements, which stifle medical innovation:

Califf’s industry ties run deep. He worked closely with drug companies in the best possible way: convincing them to do large, expensive, and, for Duke, profitable clinical trials that helped prove the effectiveness of major medicines like Sanofi’s Plavix, Merck’s Vytorin, and Johnson & Johnson JNJ Xarelto. But he has not been a pushover, ever, and his goal has always seemed to be to make sure that doctors and patients have the best evidence possible for deciding what drugs to give to patients. He has not always been easy on industry.

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.

“I can’t imagine a situation, given what we know now, other than a screening mechanism followed by some sort of trial for the net risk and benefit versus risk,” Califf said at the time.

Industry has hated these trials, arguing that they are preventing new diabetes drugs from being developed.

It can be fully expected that the FDA will continue to move away from the safety and effectiveness standard and demand outcomes and survival data routinely with the new leadership and in response to other unfortunate medical issues that will invariably happen with new marketed drugs as more and more experience is obtained with their use. Dr. Califf was asked this direct question at the Senate HELP (Health Education Labor and Pensions) Committee hearings on his nomination as new FDA Commissioner on November 19, 2015:

In one pointed exchange, Warren asked Califf about the propriety of clearing therapies at such a rapid rate, once again referencing Califf’s ties to the industry. "Your relationships also raise concerns about your motivations," said Warren. "Do you agree with arguments to lower standards for FDA approval of drugs and devices?"

"I have never been a proponent of lowering standards for anything," Califf shot back. "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."

When the FDA, understandably does retrace and tries to protect itself by making the drug approval hurdles higher in response to public ridicule and accusations of poor job performance hurled at them at Congressional hearings, Congress does not do its job. It does not perform the proper oversight to re-instruct the FDA that its mission is to promote health as defined in the statute (“to promote health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion”). Through oversight, Congress doesn’t re-direct the FDA to uphold safety and effectiveness as the standards for approval, and reinforce least burdensome approach (for devices). And, Congress actually aids the FDA in preferring to approve drugs for niche diseases at the expense of diseases that affect large populations of patients by passing laws like FDASIA (Breakthrough Therapy Designation) and 21st Century Cures (Priority Review for Breakthrough Devices and many other provisions), which largely focus on orphan conditions, those affecting less than 200,000 patients per year.

And so, the vicious cycle: (1) external events, such as the emergence of public health crises (ebola, HIV, methicillin-resistant staphylococcal infections) and adverse events of approved products call into question the adequacy of FDA’s approval policies; (2) poor Congressional oversight (publicly humiliating the FDA when products are associated with undesired events); (3) FDA retrenchment in the form of disproportionate focus on pre-approval requirements as opposed to post-approval vigilance, and redirecting efforts to specific areas at the expense of others; (4) lack of Congressional oversight to force the FDA to comport itself in accordance with original laws when the FDA understandably shies away from its directives to promote health, and (5) passing of unnecessary and contradictory laws (initiated a/o supported by the FDA) that cement the alternative approach the FDA has taken, which conflicts with Congress’ original intent, and stymie medical innovation. (continued on pg. 8)...
The law provides for a balance between pre-approval hurdles and post-approval vigilance 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 postmarket studies and controls. The law also permits the FDA to demand post-approval studies as conditions of approval, and after products have been on the market. Moreover, the FDA has broad powers after drugs are approved to exercise enforcement by imposing restrictions, revising labeling, and executing injunctions and drug seizures; it can also charge companies that do not comply with its directives with misdemeanors (where intent need not be established) and felonies. Therefore, shifting emphasis to pre-approval requirements is not needed:

a. 513(a)(3)(C) - In making a determination of a reasonable assurance of the effectiveness of a device for which an application under section 515 has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls;

b. 505(k)(3)(C) - ESTABLISHMENT OF THE POSTMARKET RISK IDENTIFICATION AND ANALYSIS SYSTEM - The Secretary shall, not later than 2 years after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, in collaboration with public, academic, and private entities—(i) develop methods to obtain access to disparate data sources including the data sources specified in subparagraph (C); (ii) develop validated methods for the establishment of a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including, in aggregate—(I) at least 25,000,000 patients by July 1, 2010; and (II) at least 100,000,000 patients by July 1, 2012; and (iii) convene a committee of experts, including individuals who are recognized in the field of protecting data privacy and security, to make recommendations to the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of, postmarketing data specified under subparagraph (C), including recommendations on the development of effective research methods for the study of drug safety questions.

c. 505(o) - POSTMARKET STUDIES AND CLINICAL TRIALS; LABELING; (3) STUDIES AND CLINICAL TRIALS.—(A) IN GENERAL.—For any or all of the purposes specified in subparagraph (B), the Secretary may, subject to subparagraph (D), require a responsible person for a drug to conduct a post-approval study or studies of the drug, or a post-approval clinical trial or trials of the drug, on the basis of scientific data deemed appropriate by the Secretary, including information regarding chemically-related or pharmacologically-related drugs. (B) PURPOSES OF STUDY OR CLINICAL TRIAL.—The purposes referred to in this subparagraph with respect to a post-approval study or post-approval clinical trial are the following: (i) To assess a known serious risk related to the use of the drug involved. (ii) To assess signals of serious risk related to the use of the drug. (iii) To identify an unexpected serious risk when available data indicates the potential for a serious risk. (C) ESTABLISHMENT OF REQUIREMENT AFTER APPROVAL OF COVERED APPLICATION.—The Secretary may require a post-approval study or studies or post-approval clinical trial or trials for a drug for which an approved covered application is in effect as of the date on which the Secretary seeks to establish such requirement only if the Secretary becomes aware of new safety information.

d. 505(p) - RISK EVALUATION AND MITIGATION STRATEGY: (1) IN GENERAL.—A person may not introduce or deliver for introduction into interstate commerce a new drug if—(A)(i) the application for such drug is approved under subsection (b) or (j) and is subject to section 503(b); or (ii) the application for such drug is approved under section 351 of the Public Health Service Act; and (B) a risk evaluation and mitigation strategy is required under section 505-1 with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under section 505-1, including requirements regarding assessments of approved strategies. (2) CERTAIN POSTMARKET STUDIES.—The failure to conduct a postmarket study under section 506, subpart H of part 314, or subpart E of part 601 of title 21, Code of Federal Regulations (or any successor regulations), is deemed to be a violation of paragraph (1).

Proper Congressional oversight is essential to demand that the FDA use post-approval controls in lieu of more onerous pre-approval requirements. The vicious cycle of improper Congressional oversight is responsible for the progressive deterioration of the safety and effectiveness standard in deference to more onerous clinical utility and disease outcomes and survival endpoints. (continued on pg. 9)
A direct sequela of this vicious cycle is the rise of specialty pharmaceutical products, those intended for small populations of patients. 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—not 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 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.).

...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, 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.” (continued on pg. 10)
Another upshot of Congress not performing appropriate oversight is the passage of an increasing number of laws, many of which are redundant. Neither the FDA nor industry can keep pace. The fact that the 21st Century Cures Act includes provisions for training FDA reviewers on least burdensome approach validates what many have observed over the last several years in dealing with FDA reviewers – due to great turnover at the agency, new reviewers are not knowledgeable of the law, especially the fundamental bedrock grounding principles of the law. Rather, they are trained, with other personnel, on the new laws that Congress passes. And, because of the new and changing laws and difficulties in dealing with the FDA, industry is spending more on regulatory affairs. A 2012 study found that:

Top 50 pharmaceutical companies have increased their regulatory affairs budgets by an average 27% since 2010. Small drug manufacturers, as well as medical device companies, also increased their regulatory affairs budgets during the same timeframe.

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with the observation that “administration of a statute is, properly speaking, an extension of the legislative process.”

Oversight, in brief, is crucial to the lawmaking process. Only by investigating how a law is being administered can Congress discover deficiencies in the original statute and make necessary adjustments and refinements. As a Senator stated, “We must do more than write laws and decide policies. It is also our responsibility to perform the oversight necessary to insure that the administration enforces those laws as Congress intended.”

But, Congress had not been exercising “continuous watchfulness” with respect to FDA in its mission to promote health through the review and approval of new medical products.

Notwithstanding James Madison’s words regarding the power of the purse in Congressional oversight, Congress does not effectively wield this power principally because only 55% of the FDA is funded by taxpayer dollars. Approximately 45% of FDA’s 2016 budget of $4.74 billion is paid for through user fees; for fiscal year 2016, the user fees include $2,374,200 for an NDA (New Drug Application), $261,388 for a PMA (Pre-Market Approval Application) and BLA (Biologics License Application), and $5,228 per 510k. It appears that Congress has relinquished oversight to the biopharma and medical device industries, (continued on pg. 1)
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however, fear of the FDA and of repercussions from publicly criticizing the FDA render this form of oversight ineffective. But, PDUFA and MDUFA have definite performance targets for FDA. The problem has been that Congress has allowed the FDA to produce its own scorecard and set its own objectives with respect to PDUFA/MDUFA goals, which do not accurately portray FDA performance. Therefore, with respect to user fee re-authorization, we recommend the following:

1. A Government Accountability Office (GAO) investigation of FDA performance with respect to review times under PDUFA/MDUFA, accounting in calendar days. This would include anonymous industry surveys that would ferret-out the appropriateness of FDA review day determinations (based on major deficiency letters and amendments to new product applications and other mechanisms that extend the review clock). The GAO would also be asked to prepare a standard report template for FDA performance parameters that is comprehensible and grounded in real-world metrics, for example, calendar days.

2. 2017 User Fee Reauthorization provisions:

   a. As a condition of the legislation, Congress should withhold FDA PDUFA and MDUFA funds until NDA, BLA, PMA, and 510k performance targets are achieved. Alternatively, companies could be refunded for applications that are not reviewed within target time frames (1% reduction in user fees per day exceeding review period limit. For small companies, a transferrable tax credit of $10,000 per day of delay.)

   b. The FDA should be required to make yearly reports to Congress on review time performance in calendar days; and, Congress should conduct yearly hearings on FDA performance.

   c. Quarterly reports to Congress by the FDA ombudsman’s office (which should report to the Commissioner, not to the FDA center directors) regarding grievances that have been raised by companies in the FDA review of their products. Perhaps, if, as a matter of law, Congress were made aware of problems as they occurred, proper oversight would follow. Also, this would protect industry from FDA repercussions.

Unfortunately, proper oversight, alone cannot make-up for the problems that have been caused because of the lack of effective Congressional oversight for many years. Therefore, other provisions must be included in the user fee reauthorization to essentially re-set the FDA on the foundations that were established prior to the user fee era:

1. Restatement of promoting health as the FDA’s principal function with respect to new products. The law states the following as the FDA’s mission: “to promote health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion.” Of course, protecting health is part of promoting health, however, the FDA has elevated “protecting” health 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 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 [see 21 USC 355(d) Grounds for refusing application; approval of application; “substantial evidence” defined]. 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 postmarket 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 (continued on pg. 12)...
measures used to determine effectiveness and claims will be limited to the specific findings. The FDA can be permitted to establish
categories of approval according to the nature of the evidence used to support effectiveness, and if sponsors so desire to obtain
additional, “higher order,” categories (for example, survival and disease outcomes), supplemental approval applications can be
submitted.

3. 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 QIDP should remain.]

4. 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 are not shown to have improved disease outcomes and survival in post-approval
studies.

5. 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. The 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. 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, that is, whether to use the drugs in real-world patients.

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 starts a vicious cycle that stifles medical innovation: poor oversight > lack of oversight > regulatory drift >
redundant and contradictory laws > poor oversight... 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 marketplace – 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.

According to Mr. Oleszek:

The rise of the administrative state (the plethora of federal departments, agencies, commissions, and boards) has produced a
cJudiciary has produced a policymaking rival to Congress. Administrators do more than simply “faithfully execute” the laws according to congressional
intent (which may be vague). Federal agencies are filled with knowledgeable career and non-career specialists who, among
other things, write rules and regulations that have the force of law; enforce the rules via investigations and inquiries; formulate
policy initiatives for Congress and the White House; interpret statutes in ways that may expand their discretionary authority or
undermine legislative intent; and shape policy development by “selling” their ideas to lawmakers and committees via the
hearings process, the issuance of agency reports, and in other ways. The large role of the executive branch, whose activities
affect nearly every citizen’s life, underscores the critical role of oversight in protecting the policymaking prerogatives of
Congress and holding administrative entities accountable for their actions and decisions.

No government regulatory agency wields more power than the FDA, which regulates 25% of the US economy. It has amassed more
and more power largely through the expanding body of FDA law passed by Congress and regulations and guidance documents
that it issues. As we have seen with each PDUFA and MDUFA reauthorization legislation, passing more laws does not change the
behavior of the FDA – only Congressional oversight can ensure that the FDA comports itself with the letter (continued on pg. 13)...
and intent of the original laws.

Congress must do a better job of FDA oversight if the scientific discoveries that are being made at an accelerated pace are to be quickly developed into products that can affect the lives of patients today.

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