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The Prescription Drug User Fee Act: History and Reauthorization Issues for 2012

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Abstract: *Beginning in the 1990s, the Food and Drug Administration (FDA) made significant progress in reviewing applications for new drugs and medical devices in a timely manner, but under the most recent reauthorization of the Prescription Drug User Fee Act (PDUFA), the review process has become increasingly unpredictable, uncertain, and inefficient. This harms both patients, who are denied access to life-saving drugs, and the companies that research and develop these products. Congress should use the upcoming PDUFA reauthorization to refocus the FDA on its primary mission and to transform it into a 21st-century information-driven regulatory body that can keep pace with the rapid developments in medical science.*

In 2012, Congress will take up the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA), which was first enacted in 1992. This bill will affect millions of American consumers and patients. Although the Food and Drug Administration (FDA) used to be a model for drug approval around the world, today its policies and organizational structure lack predictability, certainty, and efficiency. PDUFA reauthorization should be a priority for 2012 not only for reasons relating to its original establishment, but also as a vehicle to bring the FDA into the 21st century and reversing the slowdown of drug development through transparency and partnership.

The Administration and Members of Congress should realize the impact that overarching and

Talking Points

- The Prescription Drug User Fee Act (PDUFA) has given Americans timely access to life-saving new drugs by providing the FDA with the resources it needs to review new drug applications.
- However, drug development has recently slowed. In the upcoming reauthorization, Congress needs to make core changes to the PDUFA to improve predictability, timeliness, transparency, and flexibility.
- Establishing an enhanced review model for marketing approval, advancing the use of regulatory sciences, establishing a risk-benefit grid to guide drug approvals, and standardizing risk evaluation and mitigation strategies (REMS) would enable the FDA and industry to reverse the recent decline in drug developments and approvals—ultimately benefiting the American public.
- PDUFA V could lay the groundwork for transforming the FDA into a 21st-century information-driven regulatory body. The FDA needs to have a scientific base in order to create flexible regulations that keep pace with industry's advances.

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unnecessary regulations have on biopharmaceutical research and development, which in turn affect the U.S. economy and its competitiveness in the global economy. An ambiguous and inconsistent approval process prevents Americans from accessing new therapies and drugs that save lives. The medical product development path in the U.S. has become more challenging, costly, and unpredictable as the previous reauthorizations have piled on regulations that detract from the FDA's primary task of providing innovative medical products to the American public as quickly and safely as possible.

The PDUFA gives the FDA authority to collect user fees from pharmaceutical manufacturers to fund reviews of drug and biological products marketing applications in a timely and efficient manner. With each reauthorization over the past two decades, Congress has given the FDA more power to regulate and monitor prescription drugs and biological products that are marketed to the American public. However, the FDA has fallen back on its end of the bargain. Although the PDUFA reduced the backlog of applications and limited the time an application waited for approval, FDA performance has lagged in recent years, hurting American patients and the economy. The United States cannot afford continued regression in this area. Congress needs to use PDUFA reauthorization to place the FDA on a regulation path that is information-driven and can keep pace with advances in medical science.

To return predictability to the review process, refresh the FDA and industry partnership, and allow innovation to flourish, the PDUFA reauthorization debate in 2012 needs to address four key issues:

1. Enhancing the review model for drug and biologic marketing approval,
2. Providing resources to the FDA to further develop its regulatory sciences,
3. Establishing a risk–benefit grid to guide approval, and
4. Standardizing the risk evaluation and mitigation strategy (REMS).

In addition, Congress should consider extending the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) and easing the current conflict-of-interest rules. Throughout the reauthorization discussions, Congress should keep in mind the primary mission of PDUFA: providing innovative medical products to the American public as quickly and safely as possible. Congress should pass a clean PDUFA reauthorization and avoid using it as a vehicle for unrelated legislative initiatives.

Delays in the Drug Approval Process

In the 1980s, as FDA regulations tightened and science advanced, the time required for a New Drug Application (NDA) or Biological Licensing Application (BLA) to move through FDA's opaque approval process increased significantly. The average time from submission to decision was 29 months.[1] This came to be known as the "drug lag" because drugs received approval in Europe years before they were approved in the United States. The FDA's understaffing and inability to hire scientists and experts to review applications as a result of insufficient funds contributed to these delays.[2]

The delays hurt both the manufacturers and consumers. When PDUFA was first enacted, a one-month approval delay cost manufacturers an average of $10 million.[3] Additionally, the 20-year patent life of a pharmaceutical product begins even before

1. U.S. Food and Drug Administration, "FY 1995 PDUFA Performance Report," updated February 4, 2011, at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm117257.htm* (September 22, 2011).
2. Susan Thaul, "The Prescription Drug User Fee Act (PDUFA): History, Reauthorization in 2007, and Effect on FDA," Congressional Research Service *Report for Congress*, June 27, 2008, at *http://assets.opencrs.com/rpts/RL33914_20070712.pdf* (December 6, 2011).
3. Philip J. Hilts, "Plan to Speed Approval of Drugs: Makers Would Pay Fees to U.S," *The New York Times*, August 11, 1992, at *http://www.nytimes.com/1992/08/11/business/plan-to-speed-approval-of-drugs-makers-would-pay-fees-to-us.html* (September 22, 2011).

clinical trials start.[4] Thus, the longer the FDA holds an application for approval, the less time the manufacturer has to recoup its investments in developing the product. Such delays naturally tend to discourage further innovation.

Delayed drug approvals also cause consumers and patients to suffer. "For patients with a rare or incurable condition, especially those with few or no treatment options, restricting access to a new drug is potentially devastating."[5] While an application waits for FDA review, patients are denied promising new drugs that could treat chronic, debilitating, or fatal diseases and conditions. The extent to which potentially life-saving drugs are stuck in the application pipeline and patients find themselves prisoner to regulatory delay takes away the only hope of life for many.

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Evolution of PDUFA

In response to both private and public stakeholders' growing frustrations, Congress passed the PDUFA in 1992 to expedite the drug approval process by increasing FDA funding for reviewing applications. The legislation was not intended to change the outcomes of reviews, but to accelerate decisions to approve or disapprove applications.

The law established three fees:

- **Application review fees.** A fee paid by the drug sponsor, usually the manufacturer, for review of each NDA or BLA submitted.
- **Establishment fees.** Annual fees paid by manufacturer for each of their establishments (facilities).
- **Product fees.** An annual fee for every product covered by the PDUFA.

Each fee provides about one-third of the total fees collected by the agency. Congress specified on what the fees could be spent. Most of the collected fees were used to hire additional staff to review applications.[6] At its genesis in 1993, user fee rates were $100,000 per drug. Fiscal year (FY) 2012 application review fees are $1,841,500 per drug—an increase of nearly $300,000 over FY 2011.[7]

In exchange for these fees, Congress set two conditions. First, time targets for FDA reviews were put in place—in other words, performance goals for the agency. Second, user fee revenues would supplement, not replace, congressional appropriations funding for the FDA. Congress also established two triggers or statutory conditions that must be met before collecting user fees. The first requires that Congress fund the FDAs at least at pre-PDUFA funding levels, adjusted for inflation.[8] The second trigger requires the FDA to spend at least as large a share of its congressionally appropriated funds on the approval process for NDAs and BLAs as it did in 1992.[9]

4. Michael E. Gluck, "Federal Policies Affecting the Cost and Availability of New Pharmaceuticals," The Henry J. Kaiser Family Foundation, July 2002, p. 6, at *http://www.kff.org/insurance/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=14078* (September 26, 2011).
5. Marc Boutin, "PDUFA V: Medical Innovation, Jobs, and Patients," testimony before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, July 7, 2011, at *http://democrats.energycommerce.house.gov/sites/default/files/image_uploads/Testimony_HE_07.07.11_Boutin.pdf* (October 14, 2011).
6. Donna Vogt and Blanchard Randall IV, "The Prescription Drug User Fee Act: Structure and Reauthorization Issues," Congressional Research Service *Report for Congress*, October 7, 2002, at *http://opencrs.com/document/RL31453/2002-10-07/download/1005/* (December 6, 2011).
7. U.S. Food and Drug Administration, "Prescription Drug User Fee Rates for Fiscal Year 2012," *Federal Register*, Vol. 76, No. 147 (August 1, 2011), pp. 45831–45838.
8. Vogt and Randall, "The Prescription Drug User Fee Act."
9. Susan Thaul, "The Prescription Drug User Fee Act (PDUFA): Background and Issues for PDUFA IV Reauthorization," Congressional Research Service *Report for Congress*, July 12, 2007.

PDUFA Reauthorizations

Over the past two decades, Congress has reauthorized the PDUFA four times. Each reauthorization maintained the basic structure of the law, but also increased the FDA's oversight of pharmaceutical companies, mandated tighter performance goals, and attempted to enhance transparency in the drug review process.

PDUFA I (FY 1992–FY 1997): Eliminating Backlogs and Reducing Review Time. Under PDUFA I,[10] user fees were authorized to be collected and used only on activities directly related to the application review process from submission to decision. With the additional resources to hire staff and clear application backlogs, the FDA achieved its performance goals of completing reviews of 90 percent of priority applications within six months and 90 percent of standard applications within 12 months.[11]

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The FDA may grant a waiver or exemption from the application review fee. Those who qualify for fee waivers and exemptions include small businesses submitting their first NDA or BLA, businesses that can show that paying the fee would be a financial burden, and companies submitting an NDA for an orphan drug,[12] a drug that would address a public health need, a generic drug, or an over-the-counter drug that is not associated with a new drug.[13] Waivers are not granted for the other two PDUFA fees.

PDUFA II (FY 1998–FY 2002): Increased Communication and Sound Advisory Committees. PDUFA II[14] tightened performance goals (90 percent of standard applications within 10 months) and increased reviewer responsibilities. The reauthorization implemented additional interaction requirements between the FDA and manufacturers during drug development to facilitate a smoother drug development process and help manufacturers submit more complete applications, which allow for speedier reviews. It also expanded use of prescription drug user fees to Investigational New Drug (IND) applications (pre-marketing application for pre-clinical testing approval) through the review of NDAs and BLAs.[15] As a means to approve drugs for serious or life-threatening conditions more quickly, surrogate endpoints were also approved for fast-track products. Surrogate endpoints, also referred to as biomarkers, include reduced tumor size or cancer cell count, changes in cholesterol levels, blood pressure, serum levels, or CD4 (T-cell) count as measures of drug efficacy as opposed to five-year survival rate.

Under PDUFA II, the FDA was required for the first time to establish scientific advisory committees responsible for providing expert advice and recommendations to the agency on research, clinical investigations, and marketing approval.[16] For every drug reviewed, each committee must have at least two members of the scientific community who are specialists in the particular disease or condition that the drug is designated to treat.

10. The Prescription Drug User Fee Act of 1992 (PDUFA), Public Law 102–571.
11. Susan Thaul, "The Prescription Drug User Fee Act (PDUFA)," p. 3.
12. An orphan drug treats rare disorders with a potential market of less than 200,000 individuals. Without the waiver, manufacturers would incur financial losses in developing drugs for rare disorders.
13. U.S. Food and Drug Administration (FDA), "Frequently Asked Questions on Prescription Drug User Fees (PDUFA)," updated February 23, 2011, at *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069943.htm#P159_12537* (September 27, 2011).
14. The second iteration of PDUFA was reauthorized under Title I of the Food and Drug Administration Modernization Act (FDAMA), Public Law 105–115.
15. Food and Drug Administration Modernization Act of 1997, Public Law 107–115.
16. Covington and Burling, "Food and Drug Administration Modernization Act of 1997," December 12, 1997.

PDUFA III (FY 2003–FY 2007): Fine-Tuning the Process. The third reauthorization of PDUFA[17] expanded the scope of user fees again and instituted several initiatives to improve manufacturers' application submissions. It allowed the FDA to use fees on post-market activities, such as post-approval safety surveillance and risk management up to three years after approval for drugs marketed after October 1, 2002.[18] Additionally, fees could be used on pre-clinical (pre-human testing) development activities. First-cycle preliminary reviews were established as a means for further communication between the FDA and sponsors to make the process more transparent.

With biotechnology advances during this time, biotech companies became increasingly worried that the FDA would not have the expertise to review applications for their cutting-edge biological products. PDUFA III empowered biotechnology companies to request that the FDA hire an independent consultant to assist in reviewing protocols for clinical studies in early parts of the development phase. The biotech company would be responsible for the costs of contracting an outside expert, but felt more confident that having an expert reviewing their study designs with the FDA would result in smoother and faster reviews.[19]

PDUFA IV (FY 2008–FY 2012): Safety First. After the Vioxx scandal in the early 2000s, pharmaceutical safety concerns heightened among consumers and other stakeholders. Both the FDA and consumer organizations called for strengthening the FDA's post-approval safety monitoring. As a result, calendar and time limits on post-approval activities were eliminated, allowing the FDA to use user fees to monitor drugs during their entire lifetime.

PDUFA IV further increased the FDA's clout over drug safety[20] by calling for employing risk evaluation and mitigation strategies on pre-approved drugs that warrant further safety protocols. REMS is a strategy to mitigate known or serious risks associated with a certain drug to ensure that clinicians use the drug only when the benefits likely outweigh the risks. REMS may include a medication guide, a patient package insert that explains safety concerns and elements to assure safe use, a communication plan, or an implementation system.[21] Although the reauthorization did not require all drugs to follow REMS, the FDA can request REMS for drugs already on the market if new safety information arises.[22] REMS seemed to overshadow the legislation's intended purpose as application performance goals were placed on hold for one year after the fourth reauthorization to deal with REMS issues.

The fourth reauthorization also addressed advisory committee members' conflicts of interest. It imposed more stringent policies on conflicts of interest among committee members, arguably preventing the most knowledgeable scientists and specialists in the field from sitting on advisory committees.

PDUFA's Success

The approval time for NDAs and BLAs has declined since the PDUFA was enacted. The mean approval time for new molecular entities (NMEs) during PDUFA I (1992–1997) was 18.6 months. This was a significant decrease from the mean of 29

17. The third iteration of PDUFA was passed as Title V of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Public Law 107–188.
18. Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Public Law 107–188.
19. Vogt and Randall, "The Prescription Drug User Fee Act."
20. The fourth iteration of PDUFA was passed as Title I of the FDA Amendments Act of 2007, Public Law 110–85.
21. U.S. Food and Drug Administration (FDA), "Approved Risk Evaluation and Mitigation Strategies (REMS)," updated September 2, 2011, at *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm* (September 27, 2011).
22. Jill Wechsler, "FDAAA Empowers FDA to Have Greater Control over Drug Safety," *Formulary*, December 1, 2007, at *http://formularyjournal.modernmedicine.com/formulary/Policy+News/FDAAA-empowers-FDA-to-have-greater-control-over-dr/ArticleStandard/Article/detail/479293* (December 1, 2011).

months during the late 1980s.[23] PDUFA II (1998–2002) saw a mean approval time of 13.42 months for standard applications, while average approval time during PDUFA III (2003–2007) was even lower at 12.92 months.[24] The backlog of applications in pre-PDUFA years was eliminated. Additionally, as a result of PDUFA, 50 percent of new drugs created in the world are first marketed in the United States, compared to only 8 percent before the legislation.[25]

Although the PDUFA has clearly reduced drug review times, FDA performance is slipping again, and the review process is becoming more uncertain. Under PDUFA IV, review times have begun increasing. In FY 2008, average review time rose to 16.2 months—a 28 percent increase from FY 2003–FY 2007.[26] Although 80 percent of applications were eventually approved, less than half were approved during the first submission cycle.[27]

Although the PDUFA has clearly reduced drug review times, FDA performance is slipping again, and the review process is becoming more uncertain.

Overall, prescription drug user fees have facilitated a faster review process for NDAs and BLAs by providing the FDA with the resources to increase staff and decrease individual workload. Although FDA approvals for new biopharmaceuticals have doubled since the beginning of the PDUFA in the 1990s, drug manufacturers "face substantial challenges," according to Dr. Janice Reichert, research assistant professor at Tufts University. She notes, "While the strong growth in approvals is positive news for biotech companies and patients alike, biopharmaceutical development remains complex and developers face substantial challenges if they are to continue winning approvals at the pace of the last decade."[28] PDUFA V needs to revitalize the drug development and the approval process.

Traditional Reauthorization Issues

PDUFA legislation has received its share of support and criticism from the pharmaceutical industry, the FDA, Members of Congress, and consumer and patient advocates. Since the PDUFA IV reauthorization, FDA's performance has lagged as a result of many factors, including the agency's heavy focus on product risks rather than product benefits, which leads to extensive and costly clinical trials and longer application review times, which the companies and public can ill afford.

Traditional criticism of the PDUFA legislation includes several types of concerns: inadequate funding to cover the FDA's increasing expenses, the relationship between the FDA and the industry that is potentially too close, the appropriate balance of efficacy versus safety concerns, and conflict-of-interest policies.

23. Ernst R. Berndt, Adrian H. B. Gottschalk, Tomas J. Philipson, and Matthew W. Strobeck, "Industry Funding of the FDA: Effect of PDUFA on Approval Times and Withdrawal Rates," *Nature Reviews Drug Discovery*, Vol. 4, No. 7 (July 2005), p. 546, at *http://web.mit.edu/cbi/publications/Nat_Rev_Drug_Discovery_Berndt_etal.pdf* (September 26, 2011).
24. Calculations based on data from U.S. Food and Drug Administration, "CDER Approval Times for Priority and Standard NDAs and BLAs Calendar Years 1993–2008," updated February 24, 2009, at *http://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/drugandbiologicapprovalreports/ucm123957.pdf* (September 27, 2011).
25. Campaign for Modern Medicines, "PDUFA: In Depth," at *http://modernmedicines.com/pdufa-info.php* (December 7, 2011).
26. California Healthcare Institute and Boston Consulting Group, "Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry," February 2011, p. 11, at *http://www.chi.org/uploadedFiles/Industry_at_a_glance/Competitiveness_and_Regulation_The_Future_of_America%27s_Biomedical_Industry.pdf* (September 27, 2011).
27. U.S. Food and Drug Administration, "FY 2010 PDUFA Performance Report to the President and Congress for the Prescription Drug User Fee Act," 2010, p. 4, at *http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf* (October 25, 2011).
28. Janice Reichert, "Biopharmaceutical Product Approvals in the U.S. Rose Dramatically in 2000s," Tufts Center for the Study of Drug Development *Impact Report 2011*, Vol. 13, No. 3 (May/June 2011).

Funding. Although user fees have increased each year, Congress has been reluctant to increase its direct appropriations. Thus, while user fees accounted for only 7 percent of the costs associated with the drug review process in 1993, user fees contributed 60 percent in 2009.[29] Yet the annual upward adjustments in fees has still not been enough to cover the FDA's increased needs and workload. Some consumers are worried that the success of the user fee law has indirectly affected Congress's willingness to increase FDA appropriations. Therefore, funding will be a key issue in PDUFA V

While user fees accounted for only 7 percent of the costs associated with the drug review process in 1993, user fees contributed 60 percent in 2009.

It is important to keep in mind that PDUFA fees pay for drug reviews, not drug approvals. The biopharmaceutical industry has been open and willing to pay higher fees for a more predictable and less ambiguous drug review process. Peter Pitts from the Center for Medicine in the Public Interest notes that "a well-funded FDA is in the best interest of the both the public health and a robust biopharmaceutical industry."[30] Pitts also suggests that prescription drug user fees should be called "predictability deposit" user fees because a deposit is needed to obtain a public health return.[31]

The Industry's Influence. It has been argued year after year that the FDA relies too heavily on industry's user fees, making the FDA a captive of the industry it regulates. Hence, critics complain that the agency has insufficiently protected the public from defective and unsafe drugs. Many argue that, rather than focusing on the safety of patients, the FDA is more concerned with making the pharmaceutical companies happy because it depends on their user fees to fund much of its work.

The PDUFA exists primarily to foster a regulatory environment that is predictable and transparent, and such an environment requires a positive working relationship between the regulator and those being regulated. A partnership between the FDA and the biopharmaceutical industry is essential to creating a certain and transparent review process. The PDUFA's philosophy should be centered on an FDA and industry that work together to develop and market drugs and therapies to the public in a safe, but efficient and timely manner. Interpreting user fees as a way for industry to exercise some control over its regulator will only make it more difficult to accomplish PDUFA's ultimate goals.

Disregarding Drug Safety. The push for faster review times provokes the criticism that the emphasis on speed leads to suboptimal reviews, thus putting the public in danger of dangerous drugs. According to research performed by a group at Harvard University, the time constraints placed upon the FDA to review NDAs and BLAs result in a high proportion of application approvals occurring just a month or less before the deadline, suggesting that a rush to meet review targets jeopardizes patient safety. Their findings state "that the rate at which drugs experience post-marketing regulatory events is appreciably higher for drugs approved in the months before the PDUFA clock deadlines, compared to other drugs." [32]

The FDA culture has reverted to an earlier version that focuses more on risk than on benefits. Accusations from the media, the public, and some Members of Congress that the review process is too lax and has failed to protect the public's welfare have influenced the FDA to become even more risk adverse.

29. California Healthcare Institute and Boston Consulting Group, "Competitiveness and Regulation," p. 6.
30. Peter Pitts, "No Deposit, No Return," Center for Medicine in the Public Interest, November 29, 2010, at *http://www.cmpi.org/uploads/File/No-Deposit.pdf* (October 25, 2011).
31. *Ibid.*
32. Daniel Carpenter, Jacqueline Chattopadhyay, Susan Moffitt, Justin Grimmer, Jake Bowers, Clayton Nall, and Evan James Zucker, "Deadline Effects in Regulatory Drug Review: A Methodological and Empirical Analysis," Robert Wood Johnson Foundation *Working Paper* No. 45, October 2009, p. 23, at *http://healthpolicyscholars.org/sites/healthpolicyscholars.org/files/w45_carpenter.pdf* (September 28, 2011).

The Recent Decline in Drug Development

Since the beginnings of PDUFA, more and more resources have been funneled into the drug development process because of its increasing complexity. From the early 1990s to 2006, total spending on health-related research and development tripled.[33] However, the number of new drug approvals has not followed the same trend. FDA drug approvals shot up during the first decade of PDUFA, but declined during the second decade.

The cost to develop a new drug in 1987 was $318 million.[34] In 2001, a study performed by Tufts University researchers "estimated that total R&D cost per new drug [was] US$ 802 million in 2000 dollars."[35] More recently, in 2010, additional researchers replicating the 2001 Tufts study found "that the 'cost of drug development' (or the net revenue needed to make investment in new drugs profitable) is over $1 billion."[36] The cost and time required to shepherd a new drug through the development and approval process causes American patients to lose potential health benefits they could have received from taking the drugs sooner. One researcher estimates that a one-year delay in drug approval costs nearly 200,000 patient lives because they could not legally access novel treatments.[37]

In 1996, there were 62 NME approvals.[38] In 2006, 22 NMEs were approved by the Center for Drug Evaluation and Research (CDER) at the FDA, and in 2010, only 21 NMEs were approved.[39] In 2011, a record low number of products entered the FDA approval process, while a high number of products favorably completed the process.[40] However, the Manhattan Institute's Paul Howard cautions that these "results should probably be taken with a grain of salt" because the numbers may not reflect the shape of the pharmaceutical research and development (R&D) pipeline. The approved drugs could have been in the development phase for many years before their applications were submitted for marketing approval.[41] It is important to note that the low number of new applications in recent years is not due solely to more onerous FDA approval requirements. Industry productivity has declined recently as developing promising candidates has become more of a struggle because the basic science has become more difficult.[42]

33. Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," October 2006, at *http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf* (December 1, 2011).
34. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, Vol. 22, No. 2 (March 2003), pp. 151–185, at *http://www.cptech.org/ip/health/econ/dimasi2003.pdf* (December 7, 2011).
35. *Ibid.*, p. 180.
36. Christopher Paul Adams and Van Vu Brantner, "Spending on New Drug Development," *Journal of Health Economics*, Vol. 19, No. 2 (February 2010), pp. 130–141.
37. John R. Graham, "Fixing the U.S. Food and Drug Administration: More Money and Power—or More Competition?" *Drug Discovery News*, July 2009, at *http://www.pacificresearch.org/press/fixing-the-us-food-and-drug-administration-more-money-and-poweror-more-competition* (October 12, 2011).
38. Berndt *et al.*, "Industry Funding of the FDA," p. 553.
39. U.S. Food and Drug Administration, "New Molecular Entity 2010 Statistics," February 8, 2011, at *http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM242695.pdf* (December 1, 2011).
40. U.S. Food and Drug Administration, "FY 2011 Innovative Drug Approvals," November 2011, at *http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM278358.pdf* (November 4, 2011).
41. Paul Howard, "FDA: Record Number of Innovative Drug Approvals in 2011," *Medical Progress Today*, November 4, 2011, at *http://www.medicalprogresstoday.com/2011/11/fda-record-number-of-innovative-drug-approvals-in-2011.php* (December 7, 2011).
42. Deloitte Centre for Health Solutions and Thompson Reuters, "Measuring the Return from Innovation: Is R&D Earning Its Investment?" 2011, at *http://www.deloitte.com/assets/dcom-unitedkingdom/local%20assets/documents/industries/life%20sciences/uk-life-sciences-measuring-the-return-from-innovation.pdf* (November 30, 2011).

The FDA deserves credit for its approval success in 2011, but to ensure 2011 does not become an outlier year in the number of new drug approvals and to further encourage pharmaceutical productivity, Congress should make significant changes to the drug approval process in the next PDUFA reauthorization.

Small Changes Are Not Enough

Although the input of resources is increasing, medical innovation is stagnating. Costs are still skyrocketing, drug failures are still occurring late in the pipeline, and patients are being denied the drugs they need. Small changes to the PDUFA in past reauthorizations have increased the size of the FDA and created excessive regulatory burdens, such as REMS, but have not made it much more productive. The FDA needs to make a paradigm shift in how it approves and regulates medical products in order to continue the trend of drug approvals seen in 2011.

The FDA is unable to keep pace with systems biology, nanotechnology, wireless health care devices, medical imaging, and cell and tissue-based products, and more and more drug research and development are based on such technology.

Instead of focusing on minor changes to improve PDUFA, Congress should use the reauthorization of the PDUFA to revamp the FDA into an agency that can handle future medical innovations and anticipate how science and drug development will evolve. How the FDA allocates its resources and handles its communication with the biopharmaceutical industry is just as important as how much funding the FDA receives through user fees. As the FDA develops tools and methodologies to strengthen the drug review process and become more productive, flexible, and predictable, clinical trial requirements may become shorter, smaller, or fewer—shortening the R&D timeline. This will then provide more incentive for the biopharmaceutical industry to increase research and development, submit more applications, and reverse the past decade of decline in developing novel medical drugs and therapies. PDUFA legislation should be used to rescue the FDA from its 20th-century mentality.

An FDA for the 21st Century

With a mission to protect and promote public health, the FDA should ensure the safety of drugs, biological products, and medical devices, while actively collaborating with industry to translate scientific findings into marketed products for public benefit. The FDA's standards guide manufacturers through the development process, and because the FDA sets the tone for medical developmental programs around the country, its standards should be up to date and predictable so safe and effective medical treatments can reach the market. The FDA's antiquated system evaluates the safety and efficacy of drugs with a rule-based checklist and little communication with the application's sponsor. This system forces regulators to use 20th-century measurement tools to evaluate medical advancements that are more personalized and information-driven.[43]

For example, the FDA is unable to keep pace with systems biology, nanotechnology, wireless health care devices, medical imaging, and cell and tissue-based products, and more and more drug research and development are based on such technology.[44] "The FDA cannot fulfill its mission because its information technology…infrastructure is inadequate."[45]

PDUFA V could lay the groundwork for transforming the FDA into a 21st-century information-driven regulatory body. The FDA needs to have a

43. Peter J. Pitts, "FDA and the Critical Path to Twenty-First-Century Medicine," *Journal of Medicine and Philosophy*, Vol. 33, No. 5 (October 2008), pp. 515–523, at *http://www.cmpi.org/uploads/File/FDA%20Critical%20Pa%E2%80%A6nal%20Article.pdf* (October 11, 2011).
44. U.S. Food and Drug Administration, "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology," November 2007, p. 4, at *http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf* (November 30, 2011).
45. *Ibid.*, p. 5.

scientific base in order to create flexible regulations that keep pace with scientific advances. Instead of focusing on the little technical details within the PDUFA legislation and nitpicking at the same issues that arise with each reauthorization, Congress needs to address the larger concerns about the FDA in order to rejuvenate medical product development. Predictability is the key to success in the PDUFA program.

PDUFA V, in particular, could achieve these goals with four overarching themes that are identified in the current draft negotiated between the FDA and industry: enhanced review model, greater emphasis on regulatory sciences, a patient-centered risk-benefit framework, and modern drug safety system.[46]

Enhanced Review Models for a Predictable Process. PDUFA reauthorization needs to return the law to the original purpose of creating a predictable development environment so manufacturers will produce innovative products that will be quickly approved by the FDA and reach the American public. The current review model for NME, NDAs, and BLAs is nontransparent, uncertain, and inefficient. Although the previous model has served the public well in the past, it will not work in the future because the drug development process is evolving. The FDA needs to adopt an enhanced review model to keep up with the advancements of the 21st century.

Biopharmaceutical manufacturers are concerned about the lack of communication during the review process, which often leads to multiple-cycle reviews of applications, increasing the time that patients are denied access to drugs and other products. With its limited resources, the FDA needs to use its time more efficiently and incorporate sponsors throughout the review process, not just at the beginning and the end as it has done in the past.

At present, after receiving an application, the FDA has no obligation to speak with the company regarding the application's progress. Previous PDUFA reauthorizations have addressed communication issues within the review process, but have not adapted the process in a way that further promotes a partnership between the FDA and companies and that makes the review process more navigable.

The PDUFA V draft agreement between the FDA and the biopharmaceutical industry of recommendations to Congress encourages sound project management. It sets milestones in the review model—pre-NDA meetings, mid-cycle meetings, and late-cycle meetings—at which the FDA would be required to communicate with manufacturers about any specific issues that have arisen in the application. This also allows sponsors to predict better when their products will be approved. Instead of waiting months to perform additional tests or provide more data to the FDA per FDA's requests, sponsors could begin gathering the additional information immediately, further reducing the time needed to review the application and decreasing the chances of needing to go through a second cycle of review.

One of the biggest issues in the drug review processes is determining how to count days toward FDA performance goals. Currently, the clock starts ticking the moment the FDA receives an application, but it is paused when the FDA reaches out to a sponsor and is waiting for a response. This way of calculating the elapsed time does not reflect the total time that an application is under review. Discussions have been underway to create a "total time" performance goal in which the clock is not paused any time after an application has been submitted.[47]

A new regulatory model that provides drug companies with transparency, clarity, and certainty is needed to continue developing innovative products without a convoluted review process. This would mark the beginning of an open and communicative FDA that strengthens its collaboration with indus-

46. U.S. Food and Drug Administration, "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017," draft, September 2011, at *http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf* (December 1, 2011).

47. Laura Uzdienski, "The Latest Developments for MDUFA III," HealthpointCapital *Orthopedic and Dental Industry News*, October 12, 2011, at *http://www.healthpointcapital.com/research/2011/10/12/the_latest_developments_for_mdufa_iii/* (October 20, 2011).

try to produce safe and effective medical products. Next step is the beginning of an information-driven FDA.

Regulatory Science for an Expedited Review Process. The United States cannot afford to have drugs in the development pipeline any longer than the current average of 15 years. In fact, this time needs to be reduced to support medical innovation and provide U.S. patients with life-saving therapies in a timely manner. The quick "fix" to this problem would be to "arbitrarily lower evidentiary standards for new products," but this would just feed the public fear of the FDA approving unsafe products.[48] The better solution would be to incorporate scientifically based methodologies and infrastructure—such as bioinformatic systems, which collect and analyze data from a plethora of sources using computers and statistical techniques, and developing and qualifying new biomarkers, which act as indicators for a particular biological state—into the developmental and review processes. This would accelerate innovation and eventually reduce the costs of medical product developments and approvals.

Current FDA policies are not set up to address the challenges from emerging science or the issues surrounding personalized medicine. The opportunities from this safer and more effective type of medicine are expanding. Medicine is moving toward a more personalized approach because the scientific community is gaining a better understanding of the physiological, chemical, and biological underpinnings of health, disease, and treatment. To capitalize on this, the FDA in collaboration with the pharmaceutical industry needs to develop better tools for communicating, data mining, and evaluating clinical trials throughout drug development. This will enable it to accomplish the overarching PDUFA goal of realizing a speedier application process that makes safe and effective medical products available to the public in a timely manner.

In order to support the future of medicine, the FDA needs a more advanced infrastructure. The FDA recently stated that its infrastructure and tools to evaluate the strategies and outcomes of personalized medicine are "underdeveloped."[49] Biomarkers, bioinformatics, trial designs, and pharmacogenomics standards need to be addressed and improved to work with industry in moving novel therapies from the lab to the bedside in the safest and quickest way possible. These techniques have the potential to break down many barriers that separate the FDA and industry and prevent them from accomplishing the PDUFA's mission.

PDUFA V needs to advance the use of biomarkers in the evaluation of new drugs and biologics, allow for new endpoints, and promote creative clinical study designs. This will help to change the drug development process from a trial-and-error system to a more predictable and personalized system that allows drugs to move through the pipeline more quickly. Additionally, these new development tools will lower the cost of research and development by helping manufacturers to identify failing products earlier in the process. According to one estimate, a 10 percent improvement in predicting the failure of products before clinical trials could save a company $100 million in costs.[50]

Science and information—not a one-size-fits-all, rule-based system—should drive the drug approval process. Existing regulations on the development of new drugs and biologics require safety and efficacy for the general population. As a result, drugs that would be safe for a small population or individual often fail the review. This regulatory environment also pushes out promising drugs that work for a broad population, but may cause adverse problems

48. Jeff Allen, "The Prescription Drug and User Fee Act: An Opportunity for Progress in Science and Innovation," *The Hill*, October 26, 2011, at *http://thehill.com/blogs/congress-blog/healthcare/189919-the-prescription-drug-and-user-fee-act-an-opportunity-for-progress-in-science-and-innovation* (October 31, 2011).
49. U.S. Food and Drug Administration, "Driving Biomedical Innovation: Initiatives to Improve Products for Patients," October 2011, at *http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM274464.pdf* (October 11, 2011).
50. Pitts, "FDA and the Critical Path to Twenty-First-Century Medicine," p. 519.

and side effects for sub-populations. The FDA's policies and regulations may have worked for drugs in the past, but will not work for drugs of the future.

Patients and clinicians do not want an FDA that simply provides its blessing to use certain drugs. They need an FDA that provides them with the information to make more informed decisions. The FDA should serve as an information provider, not merely as a gatekeeper. The more information available to physicians and patients, the greater the ability they will have to make informed, personal decisions on the medicines that they prescribe or use. A science-based approval system will simultaneously produce an information-driven system.

Under the PDUFA V agreement goals, the FDA would have the capacity to more efficiently review applications that involve complex issues, such as biomarker qualifications and pharmacogenomics. At the pace science is advancing, use of biomarkers and bioinformatics will soon be commonplace for all new drugs and biologics. These regulatory techniques not only increase the speed at which safe and effective drugs reach the public, but could also reduce development costs, further encouraging innovation and contributing to the American economy while improving the post-approval targeting and effectiveness of drug therapies.

Structured Risk-Benefit Framework

The FDA is tasked with ensuring the safety and efficacy of drugs and biologics. However, no drug is ever 100 percent safe. Even a drug as common and as well understood as aspirin can be unsafe to certain patients. Therefore, when reviewing an application for a new medical product, the FDA measures the safety of a product to ensure that the benefits outweigh the risks. A risk–benefit framework would allow for a shared understanding among the regulator, the industry, and the public on medical products.

Historically, risk–benefit assessments have been performed ad hoc and informally. The FDA, the industry, and patient advocacy groups are calling for a more structured and systematic system to learn how to evaluate different diseases, with patients playing an integral role in the policy decisions. There is no right way to do this. FDA decisions are not purely black and white, but a risk–benefit grid could set the basic parameters for interpreting and judging new drugs. A robust and systematic process for evaluating the safety of medical products would also help the FDA decision-making process and provide manufacturers with needed transparency.

First, the risk–benefit process should be patient-centered, and the PDUFA V agreement between FDA and manufacturers is designed to make this happen. The patients should be responsible for educating the agency on their risk tolerance. Often, the FDA will base their risk–benefit decisions on the opinions of a small group of medical reviewers without hearing from those who live with the disease or condition the drug will treat. Patient groups, particularly those focused on life-threatening conditions such as cancer, have strongly expressed their desire to participate in the review process because they are the ones who will be taking the drugs, not the normal consumer.

No drug is ever 100 percent safe. Even a drug as common and as well understood as aspirin can be unsafe to certain patients.

Individual patients make decisions and judgments based on their own personal feelings, preferences, and circumstances. However, in the past, the risk–benefit assessment has taken the "perspective of the greater public good," not of the individuals who would be taking the drug.[51] Some patients are willing to take greater risks than others depending on their conditions and the other therapies available to them.

Second, the framework should be flexible, allowing the process to be tailored to specific drugs and therapies. The PDUFA V agreement provides the FDA with the ability to explore methods for a more structured and qualitative risk–benefit framework to enable sponsors to understand how the FDA

51. Boutin, "PDUFA V: Medical Innovation, Jobs, and Patients."

weighs the risks and benefits of a product. Under the agreements, the FDA would be responsible for holding meetings and workshops to determine the best framework for incorporating the perspectives of patient advocacy groups into the decision-making process and establishing a structured framework for assessment. However, meetings can become an excuse for not doing something and should not be PDUFA V's answer for launching a systematic way to assess risks and benefits.

Not only is the FDA already designing a risk–benefit grid as a management tool, but multiple studies have already created standardized frameworks that could be tailored to any drug or setting, before or after approval.[52] One such framework is the Benefit Risk Action Team (BRAT), which is "a set of processes and tools for selecting, organizing, summarizing, and interpreting data that is relevant to decisions based on benefit–risk assessments."[53] A consistent framework that aids decision making, rather than relying on a mathematical equation for approval, would reintroduce predictability into the review process, which was the original purpose of the PDUFA.

Therefore, instead of just talking the talk, PDUFA V needs to walk the walk and take substantive steps to institute a risk–benefit framework that would benefit all stakeholders in the drug development and approval processes. This reauthorization needs to establish a risk–benefit grid, such as the BRAT framework, flexible enough to handle many settings and drugs, instead of moseying around establishing meetings to discuss the issue ad nauseam, ultimately delaying any decision until the next reauthorization in 2017.

Standardization of REMS. To ensure that a drug's benefits outweigh its risks, PDUFA IV gave the FDA authority to require certain drugs to incorporate REMS before being marketed. Risk management allows the FDA to bring riskier products onto the market by taking advantage of tools to improve the use of drugs with known safety risks. Regrettably, REMS has become a burden to the health care system, provoking its share of criticism.

PDUFA IV was distracted by risk mitigation, which ultimately weakened innovation. The focus on REMS regulations has been discussed as a cause of lagging FDA performance during PDUFA IV. Under PDUFA IV, user fees increased 25 percent, but the money was rerouted to risk mitigation, instead of spending it on spurring innovation. REMS is an important tool to ensure drug safety and the safe use of drugs, but it should not detract from the core purpose of PDUFA or impose burdens on health care providers.

REMS lacks a standardized framework, similar to the lack of standardization in risk–benefit assessment. The FDA does not have any scientific grounds to use one REMS over another, so different REMS strategies are used for similar risks. Health care providers, patient groups, and pharmaceutical companies want the FDA to standardize REMS for different tasks, especially given that the use of REMS for medications will likely increase. The FDA needs to be held accountable for ensuring that its chosen REMS are effective and efficient and ultimately reduce risk.

Additional Issues

In addition, Congress should consider two other FDA-related items during PDUFA reauthorization: making the Best Pharmaceuticals for Children Act and Pharmaceutical Research Equity Act permanent and easing the conflict-of-interest rules that were established by PDUFA IV.

52. Jeff J. Guo, Swapnil Pandey, John Doyle, Boyang Bian, Yvonne Lis, and Dennis W. Raisch, "A Review of Quantitative Risk–Benefit Methodologies for Assessing Drug Safety and Efficacy—Report of the ISPOR Risk–Benefit Management Working Group," *Value in Health*, Vol. 13, No. 5 (July 2010), pp. 657–666, at *http://www.ispor.org/workpaper/risk_benefit_management_guo.pdf* (November 30. 2011).
53. P. M. Coplan, R. A. Noel, B. S. Levitan, J. Ferguson, and F. Mussen, "Development of a Framework for Enhancing the Transparency, Reproducibility and Communication of the Benefit–Risk Balance of Medicines," *Clinical Pharmacology and Therapeutics*, Vol. 89 (February 2011), p. 312, at *http://cmpi.org/uploads/File/benefit-risk-journal-article.pdf* (October 25, 2011).

The BPCA and the PREA. A lack of market incentives—such as a small target population; ethical, legal, and consent concerns; difficulty of recruitment; and lower return on investment compared to adults—has led to the minimal amount of pharmaceutical research performed on children. To encourage drug manufacturers to gather data for the pediatric use of drugs, Congress enacted the BPCA in 2002 and the PREA in 2003 with five-year reauthorizations.

The two laws work in conjunction and are often referred to as a carrot-and-stick approach to expanding pediatric drug testing and improving labeling. Under the BPCA, a drug sponsor can receive an additional six-month exclusivity on its patented product in exchange for conducting pediatric studies and reports per the FDA's written request. The decision to conduct such studies is voluntary. The PREA requires drug sponsors to conduct pediatric trials on drugs and biological products and to submit sufficient data to assess its safety and effectiveness for children. The PREA also requires them to submit an application for approval of the new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration unless waived by the Secretary of the Department of Health and Human Services (HHS).[54] The PREA does not apply to drugs that qualify for the exclusivity period under the BPCA.

Working together, the BPCA and the PREA have proven to be successful tools in driving the research and development of drugs and biologics for pediatrics. From 2002 to 2005, drug sponsors volunteered to study 81 percent of the FDA's written requests for on-patent drugs, and 87 percent of the drugs that were granted market exclusivity through BPCA had label changes.[55] Since 2007, 80 products under the PREA and 50 products under the BPCA have been studied for the use in children, and the studies were followed by important labeling changes.[56] The HHS has stated that the BPCA has generated more pediatric clinical data than any other legislation or regulatory process.[57]

Working together, the BPCA and the PREA have proven to be successful tools in driving the research and development of drugs and biologics for pediatrics.

Rather than allow their current five-year sunsets to dissuade potential sponsors from investing in the infrastructure to develop and conduct clinical trials for pediatric medicines, Congress should extend the BPCA and PREA. In addition, the five-year reauthorization cycle has inhibited the FDA from creating a set of final guidelines and regulations to guide the industry through the process because each authorization changes the law. Such important and successful laws should not be allowed to expire every five years, but be extended to instill certainty and guidance into the regulatory framework.

Conflict of Interest. PDUFA IV intensified the conflict-of-interest rules and has prevented well-qualified experts—sometimes the only experts in the field—from participating in advisory committee meetings. As an indirect consequence, patients suffer because the lack of expert advice lengthens the review process, forcing patients to wait longer for promising new therapies and drugs.

Before the FDA approves an NDA or BLA, it often consults with advisory committees specific to the drug under review. These committees are mostly composed of academics and practitioners known throughout their fields. The FDA is not beholden to their advice, but often follows it. All members on the advisory committees are required to sign a release declaring no conflict of interest relating to the drug sponsor, usually the manufacturer of the drug up for approval.

54. Pediatric Research Equity Act of 2003, Public Law 108–155.

55. U.S. Government Accountability Office, "Pediatric Drug Research: Studies Conducted Under Best Pharmaceuticals for Children Act," March 2007, at *http://www.gao.gov/new.items/d07557.pdf* (November 30, 2011).

56. *Ibid.*

57. *Ibid.*, pp. 45–47.

According to the FDA, scheduled advisory committee meetings have been cancelled and application approvals have been delayed because advisory committees have lost members to onerous conflict-of-interest requirements.[58] The FDA is unable to fill its advisory committees with the needed experts. More than one in four advisory spots are vacant in the Center for Drug Evaluation and Research. During FY 2010, an average of 29.5 percent of the positions were vacant, and FY 2011 had an average vacancy rate of 26 percent—more than double the FDA's goal of 10 percent.[59]

The FDA is having difficulty staffing its advisory committees with qualified scientists who lack any conflict of interest, and the current policy is not helping. An Eastern Research Group study commissioned by the FDA found that members of standing committees who were granted waivers had "higher overall measures of expertise" than those members who were not granted waivers.[60] Given this finding, the conflict-of-interest policies are preventing the FDA from obtaining the very best expert advice. Therefore, the PDUFA reauthorization should ease the conflict-of-interest policies.

Conclusion

The pharmaceutical development and approval processes need to be transparent, predictable, timely, consistent, and flexible enough to adapt to evolving science. In PDUFA reauthorization in 2012, Congress will have the opportunity to establish an environment that welcomes and encourages medical innovation in the United States and that provides Americans with timely access to cutting-edge drugs and therapies. Congress should use the reauthorization as a vehicle to bring the FDA into the 21st century, enabling quicker, more precise evaluation of medical products for safety and effectiveness. Such reform will require more than the minimal enhancements implemented in previous reauthorizations. The PDUFA reauthorization should be a high congressional priority in 2012.

The FDA's infrastructure and capabilities need to embrace personalized medicine, and its regulations need to be transparent, flexible, and predictable to enable manufacturers to develop more products that improve and prolong the lives of Americans. The foundational core of PDUFA—quickly moving medical innovations to the market to improve and save patients' lives—should guide the reauthorization process. Predictability and a sound partnership between industry and the FDA are essential for PDUFA to reach its core goals. Taking the shortcut, as previous reauthorizations have done, will not be acceptable this time.

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58. U.S. Food and Drug Administration, minutes of stakeholder meeting on PDUFA V reauthorization, Washington, D.C., November 17, 2010, at *http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM235777.pdf* (September 29, 2011).
59. U.S. Food and Drug Administration, "Percent of FDA Advisory Committee Member Positions Vacant at the End of the Month," at *http://www.accessdata.fda.gov/FDATrack/track?program=advisory-committees&id=AdvComm-FDA-PercentVacant&fy=all* (September 29, 2011).
60. Nyssa Ackerley, John Eyraud, and Marisa Mazzotta, "Measuring Conflict of Interest and Expertise on FDA Advisory Committees," Eastern Research Group, October 26, 2001, p. iii, at *http://www.fda.gov/oc/advisory/ergcoireport.pdf* (September 29, 2011).