MANAGING PRIORITIES:
THERAPEUTIC AREA VARIATION IN FDA DRUG REGULATION

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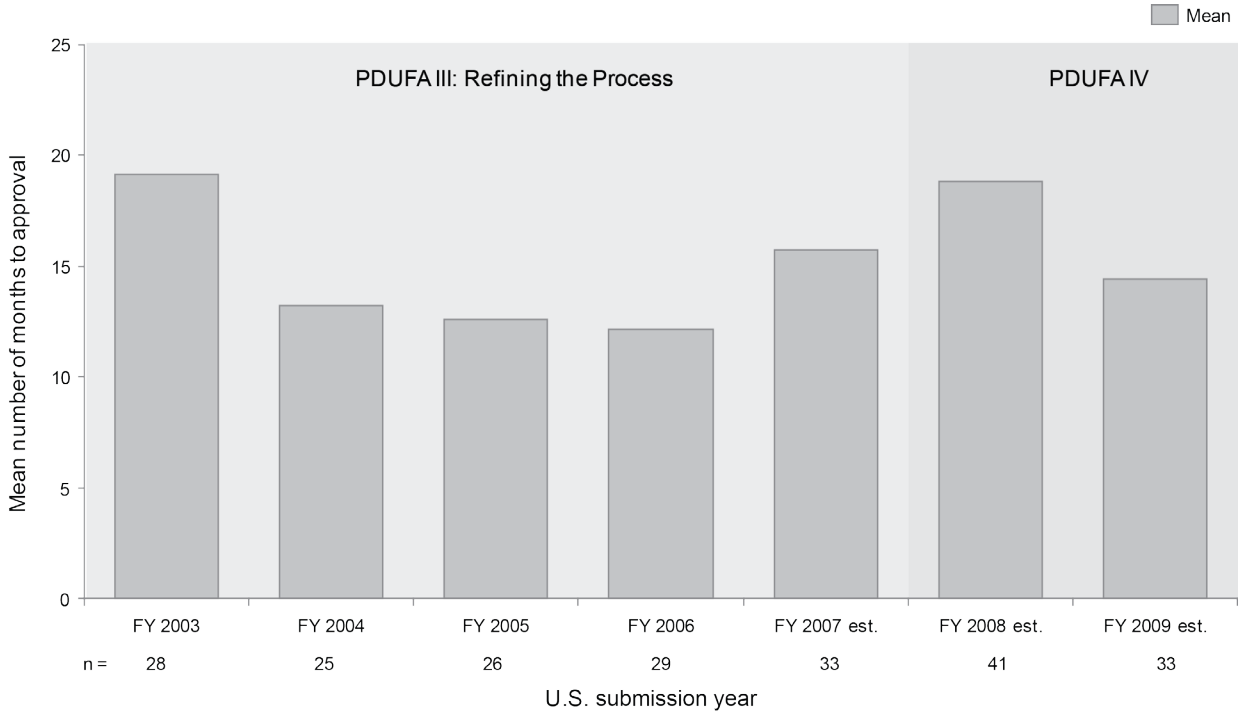
This report has two objectives. The first is to provide an update on performance of the U.S. Food and Drug Administration (FDA) with respect to its approval of drugs and biologics. This builds on our earlier study, *Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry* (2011), conducted with the Boston Consulting Group (BCG). Our second objective is to present new data that illustrate important differences in FDA performance from one therapeutic area to another. Oncology, for instance, is a high priority and the Agency has used various procedures to accelerate the approval of cancer drugs. Indeed, the FDA and others have highlighted recent approvals of oncology products as evidence of its commitment to biomedical innovation. But there are other areas with serious disease burdens – obesity and diabetes are good examples – where regulatory standards remain unclear and the Agency's performance has lagged. As Congress reauthorizes the Prescription Drug User Fee Act (PDUFA), we suggest that these discrepancies among therapeutic areas may, in fact, represent an opportunity for the FDA: namely, to replicate approaches and practices in high-performing areas throughout the Agency.

BACKGROUND: FDA DRUG REGULATION PERFORMANCE

One of the key findings published in *Competitiveness and Regulation* was a marked increase in time to approval for drugs, beginning in FY 2007 and continuing in the early part of the PDUFA IV cycle, which started in FY 2008. For example, Figure 1 shows that drugs submitted to the FDA in 2008, under PDUFA IV, experienced an average approval time of 18.9 months, a 28 percent increase over the average PDUFA III time of 14.7 months.

FIGURE 1.



Source: BCG analysis of all NME and NBE submissions, modeling of time to approval for submissions in process.

In 2009, the average drug approval time marginally improved from the PDUFA III period (by 1.3 percent) to 14.5 months. At the same time, though, the FDA failed to meet its PDUFA requirements to communicate regulatory decisions within six months for priority applications and 10 months for standard applications. Looking at new drugs submitted to the Agency in 2008, Figure 2 shows approval timelines getting longer; 45 percent of those submissions remained in process more than a year before the Agency took regulatory action. However, analysis based on a review of new drug submissions through FY 2011 suggests improvement in approval times (Figure 3).

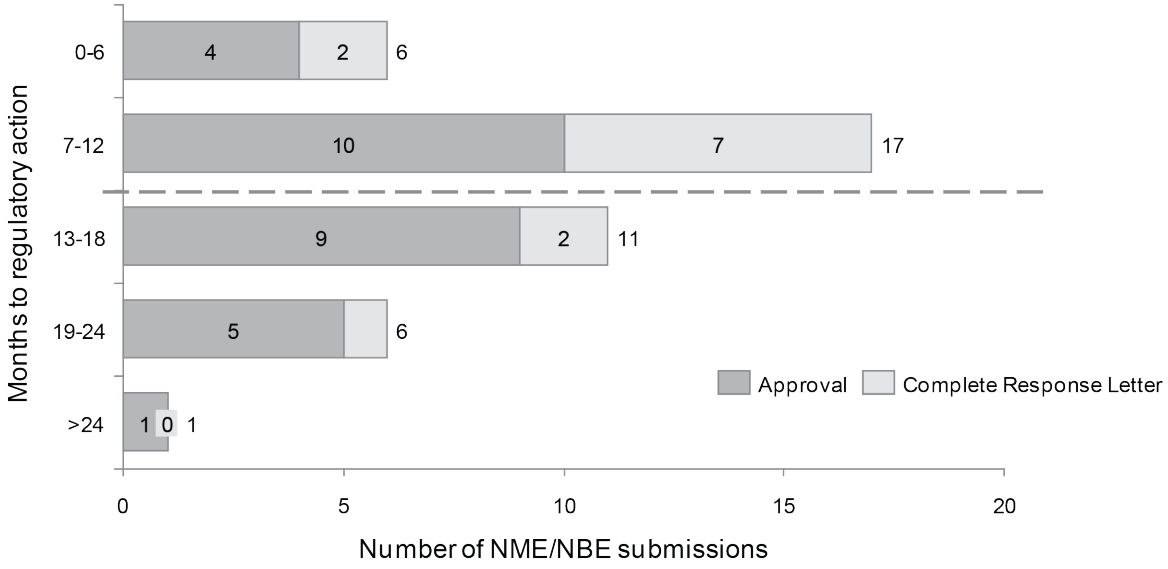
Recent data published by the Centre for Innovation in Regulatory Science in the United Kingdom showed that median approval times for drugs approved in the U.S. were shorter than those seen in Europe and Japan. In the period 2002-2011, the most important factor influencing the speed of approvals appears to have been the use of priority reviews, which accounted for 45 percent of drugs approved in America, but just 5 percent of those cleared by the European Medicines Agency (EMA). The FDA approved priority review drugs in an average of 186 days, whereas standard review times during the same period averaged 424 days.[1]

THERAPEUTIC AREA VARIATIONS

In 2011, there is evidence that the FDA began to focus seriously on improving drug approval timelines. In October, the Agency published *FY 2011 Innovative Drug Approvals*, which documented 35 "innovative" drugs cleared in FY2011, including advances in treating hepatitis C,

1 Tina Wang and Neil McAuslane, "New Drug Approvals in ICH Countries: 2002-2011," Centre for Innovation in Regulatory Science (April 2012), pp. 1, 6.

FIGURE 2.

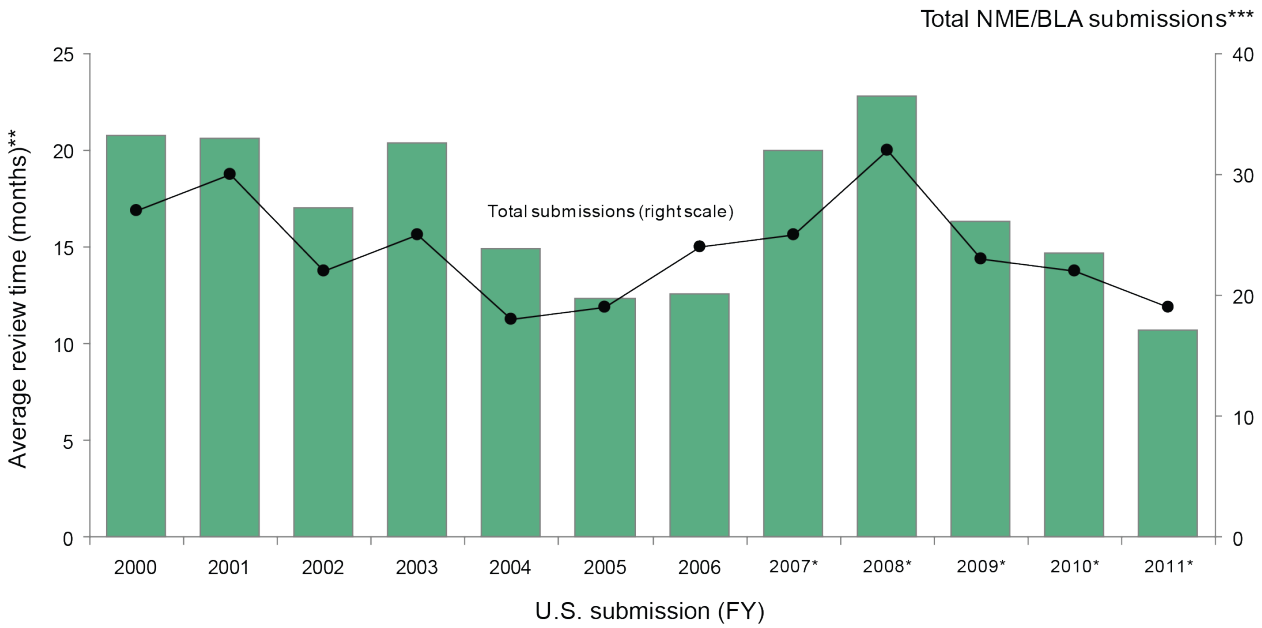


45% of submissions take >12 months to regulatory action, but 65% take >12 months to approval given CRLs

Note: Data from Drugs@FDA, EvaluatePharma. "FY 2008 Cohort" defined as any NME/NBE submissions received by FDA from October 1, 2007 through September 30, 2008. "Still in process" defined as any application that has not been approved and has not been withdrawn as of October 1, 2010. "Response" defined as receipt of Complete Response Letter or Approval Letter.

FIGURE 3.

Drug approval times have improved since '08



*Adjusted for drugs in-process by assuming review in 48 mo (2007), 36 mo (2008), 24 mo (2009), or average for therapeutic area (2010-11)
**This and all subsequent analysis of drugs excludes plasma products, imaging agents, vaccines, and ophthalmic solutions
***Does not include submissions eventually rejected
Source: FDA drug database; BCG analysis

lupus, pneumonia, and several different cancers and orphan diseases. According to the report, all but one of these drugs was approved on or before the target dates set forth in PDUFA, and the majority in their first review cycle. The Agency accomplished all this by using expedited approval pathways that, in many cases, streamlined clinical trials, allowing for smaller, shorter or fewer studies. In the same vein, earlier last year, the Friends of Cancer Research published data reflecting strong Agency performance for oncology drugs, noting that most novel oncology products have been approved in the U.S. ahead of Europe.[2]

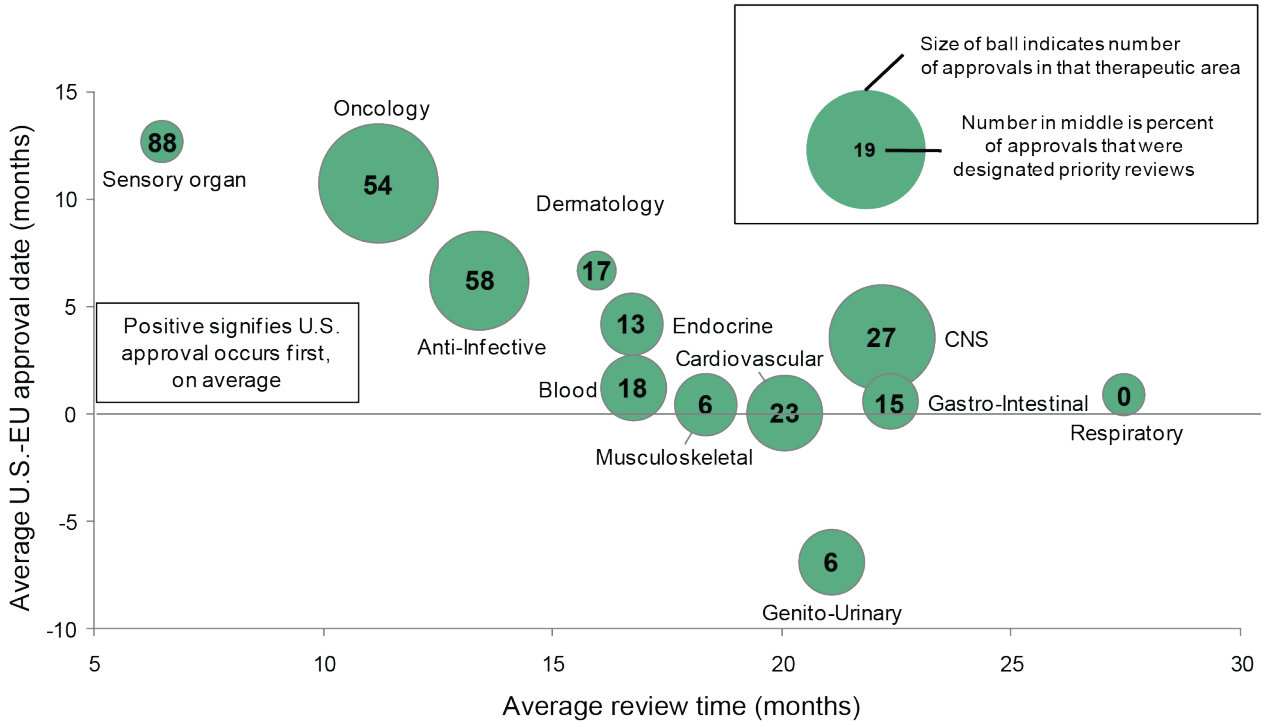
2 U.S. Food and Drug Administration, *FY 2011 Innovative Drug Approvals*, November, 2011, pp. 4-8; Samantha A. Roberts, Jeff D. Allen, Ellen V. Sigal, "Despite Criticism of the FDA Review Process, New Cancer Drugs Reach Patients Sooner in the United States," *Health Affairs*, June 2011.

These are important findings. And among therapeutic areas, oncology, infectious disease and orphan diseases are bright spots. But recent analysis of FDA data suggests a more nuanced picture. The FDA is not a monolith; there are significant deviations in review times, depending on a product's therapeutic area. As illustrated in Figure 4, between 2000 and 2011, oncology and anti-infective drugs, for example, experienced the fastest reviews, on the order of 10-15 months. For other categories – cardiovascular, central nervous system, gastro-intestinal, respiratory, etc. – average review times stretched from 20 to 30 months.

No single factor explains differences in performance among therapeutic areas. Some fields may be scientifically more complicated, with fewer biomarkers or with poorly understood mechanisms of action for novel drugs. Drugs targeting disorders

FIGURE 4.

Substantial differences in approvals across therapeutic areas



Note: Data from drugs approved since 2000; excludes those drugs without a clearly defined therapeutic area
Source: FDA and EMA websites; BCG analysis

of the central nervous system (CNS), for example, have faced especially long approval times. While disorders like Alzheimer's, Parkinson's and multiple sclerosis impose widespread suffering, their complex biology has made them notoriously elusive targets for drug development. The regulatory process seems to mirror this complexity. During a 15-year period spanning 1996 to 2010, investigators at the Tufts Center for the Study of Drug Development found that the mean clinical phase plus approval time for CNS drugs was 32 months longer than that for other drugs. For CNS drugs to complete the clinical trial process took 102.2 months, about 40 percent longer than non-CNS drugs. Meanwhile, the approval time for CNS drugs averaged 20.3 months, 13 percent longer than their non-CNS counterparts. Commenting on the difference, Tufts principal investigator Joseph A. DiMasi said, "Although I expected that CNS drug development and approval times were longer than average, I was somewhat surprised at the extent to which they were longer," adding, "I also found it surprising that non-CNS drugs were two-and-one half times more likely to receive a priority review rating from the FDA than were CNS drugs."[3]

Ideally, recognizing that the FDA must set priorities and that not all disorders pose equal threats, one would hope for basic alignment between regulation and public health. Yet, to some degree, things have gotten out of balance.

3 Tufts Center for the Study of Drug Development, "Drugs to Treat CNS Diseases Take 35% Longer to Develop than Other Drugs," March 6, 2012.

Beyond CNS disorders, diabetes, obesity, and cardiovascular disease exert enormous, and growing, damage on health. Regulatory pathways in these areas, however, are fraught with uncertainty. And the result is that fewer large pharmaceutical manufacturers are developing products for these indications, while venture funding for startups has all but disappeared.[4]

Within industry and the venture community alike, the common wisdom is that the Agency has, in certain areas, tightened its benefit-risk standards, demanding more data over longer periods. As Sanofi CEO and former chairman of the Pharmaceutical Research and Manufacturers of America (PhRMA) Christopher Viehbacher explained, "You're starting to see primary care diseases becoming somewhat neglected" in favor of specialized cancer drugs, where patients and the FDA are prepared to accept serious side-effects in exchange for potentially life-saving treatments. "To make sure we're not ignoring unmet needs in primary care, we need a lot more clarity around the risk-benefit so there's predictability when we invest in these products."[5]

Analysis of drug submissions further reflects these findings. On the one hand, as shown in Figure 5, oncology submissions have increased significantly since 2000, potentially due, in part, to the experience of more efficient and predictable review processes. On the other hand, reflecting review times and processes seen as less certain and predictable, submission of gastro-intestinal and cardiovascular products has dropped considerably over the same time period.

Whereas FDA seemingly has encouraged sponsors of oncology drugs, the Agency has given developers of diabetes and obesity drugs, for example, mixed signals. Until recently, cardiovascular outcomes studies were limited almost exclusively to cardiovascular drug development. Evaluating heart risk for non-cardiovascular therapies now requires large trials that pose steep financial and operational challenges for sponsors. Looking at the impact of FDA's 2008 guidelines for addressing cardiovascular risk of drugs for type 2 diabetes:

- Review times doubled for incretin-modulating drugs.
- The manufacturer of vildagliptin announced in June 2008, 30 months after the NDA was filed, that it did not plan a resubmission to meet FDA requirements. (The drug was approved in the EU in 2007.)
- The number of randomized patients and patient-years in NDAs increased more than 2.5 and 4 fold, respectively, since the guidelines were published.

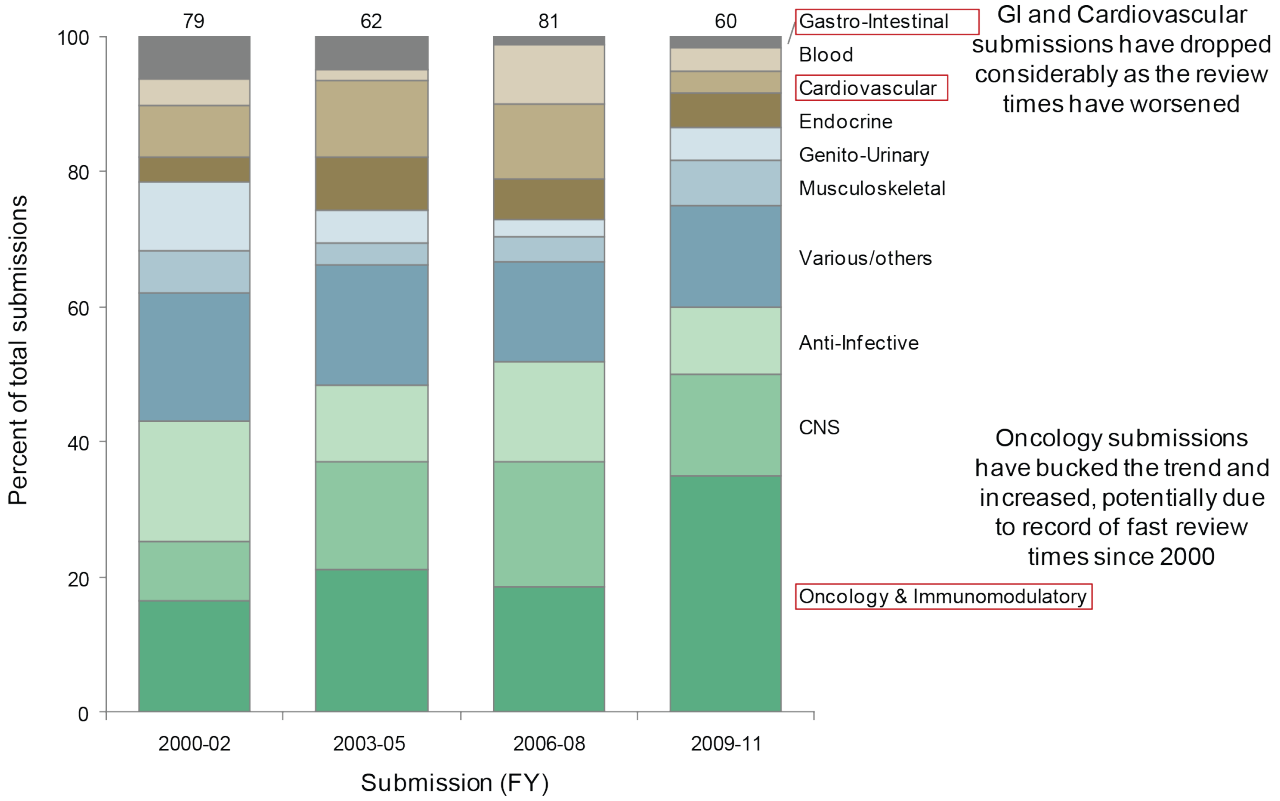
Obesity in the U.S. has reached epidemic proportions, with about one-third of adults classified as obese. Instead of taking steps to accelerate drug development, however, the Agency's Endocrinologic and Metabolic Drugs Advisory Committee recently voted to require cardiovascular risk assessments for all obesity drug candidates no matter whether preclinical or clinical studies indicated elevated risk. The panel was told that

4 National Venture Capital Association, "Vital Signs: The Crisis in Investment in U.S. Biomedical Innovation and the Imperative of F.D.A. Reform," October 2011. This survey addresses a more general attitude in the venture community: that the unpredictability of FDA regulation discourages investment in early-stage companies.

5 Ryan McBride, "Sanofi CEO Challenges FDA to Clear Up Regulatory Pathway for New Meds," *Reuters*, January 20, 2012.

FIGURE 5.

Are historic approval patterns now influencing submissions?



Source: NME/BLA database; BCG analysis

this requirement would add years to the approval process and cost sponsors an additional $100 million.[6]

For many cancer drugs, patients and the FDA have been willing to accept serious side effects and comparatively low response rates partly because there are no good alternative treatments and because patients' lives hang in the balance. Meanwhile, over the past 15 years only one obesity drug has remained on the U.S. market; all the others were withdrawn owing to post-approval cardiovascular events. This has led the Agency to reconsider its standards for clinical trials. In 2007, it issued draft guidance for obesity drugs, calling for a one-year trial with a minimum of 4,500 patients: 3,000 randomized to the treatment arm, 1,500 to placebo. As it happens, though, the dropout rate in obesity trials runs from 30 percent to 50 percent, vastly increasing the time and cost associated with enrolling enough patients to power a valid study. Thinking about risk, Sanjay Kaul, a cardiologist on the advisory panel, commented, "We as clinicians are willing to tolerate a different degree of risk depending on the benefit. If you have a drug with 5 percent weight loss versus one with 10 percent

6 C. Viereck, P. Boudes, "An Analysis of the Impact of FDA's Guidelines for Addressing Cardiovascular Risk of Drugs for Type 2 Diabetes on Clinical Development," *Contemporary Clinical Trials*, May 2011, pp. 324-32; Heidi Ledford, "Hear Studies Needed for Obesity Drugs, FDA Advisers Say," *Nature News Blog*, March 30, 2012.

or 15 percent, we might accept more risk." Still, benefit-risk assessment for obesity and diabetes products lags far behind oncology, an area where the FDA has accepted single-arm studies (trials without a randomized control group) and surrogate endpoints.[7]

Beyond medicine, diseases have a social and political dimension. And certain therapeutic areas have benefitted from coordinated efforts, aligning patient groups, medical professionals and elected officials, to elevate the importance of approving new drugs. This is clear from the legacy of the 1970s and 1980s when, first with cancer and later with AIDS, disease-oriented organizations learned how to influence the FDA: by challenging its scientific and technical expertise; by influencing its relationships with medical professionals; and by appealing directly to Congress, whose oversight and appropriations functions required the Agency's attention.

Organized advocacy on behalf of specific diseases caused the FDA to adjust its priorities. The Agency had to defend itself from critics, and it also learned to foster relationships with organized disease advocates who, it became clear, could offer crucial support. The fact that disease could represent a powerful organizing structure for the activities of patients and professionals led the Agency to develop channels for engaging them. Ultimately, in different ways, cancer and AIDS dramatically demonstrated the power of patient politics, especially in pressuring the FDA to adopt flexibility in its standards for safety and efficacy by taking into account the viewpoint of patients and the characteristics of their diseases. In equal measure, this shaped the Agency's attitude toward benefits versus risk from one therapeutic area to another.[8]

After the adoption of PDUFA in 1992, the FDA introduced the accelerated approval process. This specifically targeted drug applications for life-threatening diseases that lacked effective therapies. Largely in response to the AIDS epidemic, the Agency allowed sponsors to submit data on surrogate endpoints, rather than direct evidence of clinical benefit to patients. For AIDS drugs, the main surrogate endpoints were laboratory test results that showed suppression of HIV viral load in patients. Accelerated approvals were conditional: sponsors were required to conduct post-marketing clinical studies to validate a drug's actual clinical benefit. But the bias in favor of AIDS and cancer has endured. Since the program began, of the 81 products approved under accelerated approval, 32 have targeted AIDS, 29 cancer, and 20 all other disorders.[9]

While it is understandable that the FDA would emphasize disorders with well-organized, activist constituencies, the trouble with this approach is that many areas important to public health lack strong advocacy. Vaccines, for instance, are some of the most effective drugs in the world. But the people who benefit from most vaccines, from influenza to cervical cancer, are rarely represented by disease-oriented communities. They rarely

7 Rob Dow, "Safety Issues and Regulation Drive the Evolution of the Clinical Development Process," September 29, 2011, http://community.ppdi.com/articles/hot-topics/safety-issues-and-regulation-drive-evolution-clinical-development-process

8 Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (2010), pp. 391-402.

9 Janet Woodcock, "FDA User Fees 2012: How Innovation Helps Patients and Jobs," Statement before the Committee on Energy and Commerce Subcommittee on Health, U.S. House of Representatives, April 18, 2012, p. 7.

organize to influence vaccine approvals at the FDA. Indeed, the exception that proves the rule in this case is the AIDS Vaccine Advocacy Coalition (AVAC). Founded in 1995 and supported by leading public health organizations, including $14 million from the Bill and Melinda Gates Foundation, AVAC lobbies the FDA to streamline the development pathways for an AIDS vaccine.[10]

THE IMPORTANCE OF RELIABLE DATA

With Congress actively considering PDUFA V and additional legislation to improve the Agency's performance of its mission, there's a natural tendency to focus on the FDA's statutory authority. But, as Harvard historian Daniel Carpenter points out in his recent study of FDA drug regulation, its real power "vastly outstrips the authority and resources given to the Agency." Owing to decisions of Congress and the courts over decades, "a diminutive Agency…has been endowed with the ability to shape, accelerate, and even cut off the pipeline of new products…and with the capacity to mold the scientific methods and research agendas of thousands upon thousands of scientists and physicians throughout the world."[11]

What may be lost in technical discussions of legislation is just how much FDA performance is a function of management. History shows that, on balance, drugs targeting diseases with high profiles in the public mind and aggressive patient advocacy groups benefit more from priority reviews and accelerated approvals. Experience with cancer and AIDS suggests that legislation and formal administrative structures did not lead, but followed, managerial practices that flexibly adapted to external pressures and developing science. PDUFA V is essential to provide the Agency the core resources it needs to regulate drugs. But bringing drug approvals into better alignment with public health needs will require continuous improvements in management, infused with science and common sense. For this reason, the spirit of change reflected in the Agency's October 2011 paper, *Driving Biomedical Innovation* is encouraging.[12] The same is true of the new user fee work plans, with FDA and industry resolving to work together earlier in the development process.

Still, a time-honored principle of management is that what gets measured gets done. We have learned a great deal in working over the past two years with BCG and the FDA, mining the Agency's data in order to gain a better understanding of how it operates, and how its performance metrics have changed over time. So we believe that there is great value in (a) regularly gathering and analyzing the best possible data; (b) updating performance metrics during the next PDUFA cycle in order to track performance consistently and longitudinally; and (c) ensuring that there is agreement among the FDA, industry, and Congress that the data and how they are reported are the most accurate possible measures of Agency performance. It seems ironic that for an Agency that regulates more than 20 percent of American production, and depends increasingly on industry user fees, there has been so little in the way of consistent and robust tracking mechanisms and analysis.

10 "AIDS Vaccine Advocacy Coalition Receives $14 million from Gates Foundation," *Medical News*, August 21, 2007.

11 Carpenter, *Reputation and Power*, p. 750.

12 U.S. Food and Drug Administration, *Driving Biomedical Innovation: Initiatives to Improve Products for Patients*, October, 2011.

With respect to the regulation of drugs and biologics, FDA is, at bottom, a data management organization. The Agency requires industry sponsors to submit data from three levels of clinical studies, and it analyzes the results to decide whether a drug candidate is safe and effective. Along the way, the FDA also gathers lots of data about its own performance. We believe that reliable data are the keys both to improved decision making within the drug review process and increased efficiency across the Agency.

But identifying reliable data is harder than it sounds. In some ways, the problem reminds us of Michael Lewis's book, *Moneyball: The Art of Winning an Unfair Game* (2003). It is the story of the Oakland Athletics baseball team, focused on general manager Billy Beane, who, with a much smaller budget than most of his competitors, developed an analytical, evidence based approach to assembling a winning team. Beane's central insight was that the received wisdom of baseball professionals – players, coaches, managers, scouts and owners – about how to measure performance was deeply flawed. For a century, baseball insiders took for granted that statistics like batting average, earned run average and runs batted in were the important metrics for gauging players. Based on a novel analytic approach, Beane showed that things like on-base percentage and slugging percentage were more strongly correlated with success than traditional measures.

In a recent talk at the University of California San Francisco, Janet Woodcock, director of FDA's Center for Drug Evaluation and Research, remarked that the Agency was responsible for tracking 55,000 performance metrics; so many, she suggested, that they distracted reviewers from their primary work of approving new medicines. Certainly, anyone who has attempted to use FDA's online performance measurement tool, FDA-TRACK, has experienced its inadequacy to connect many individual process measurements with a clear sense of how the Agency performs in different areas. Perhaps, then, what is needed is a reconsideration of the collected wisdom and assumptions of FDA insiders (and many industry participants, as well). Today we have an unprecedented array of tools to collect and manage large sets of data. What is needed is for the FDA and industry to collaborate to develop innovative approaches to data that accurately reflect performance.

PDUFA V represents the next step in a successful, ongoing partnership between the FDA and industry. It is important for the legislation to remain highly focused: to support the Agency in its efforts to promote biomedical innovation; to encourage it to address areas of inefficiency; to balance its imperative to protect public safety with the importance of continuing robust private-sector investment into new drugs and biologics in order to advance public health. In the long view, public health and the economic health and competitiveness of the biomedical industry are two sides of the same coin. Without immense investment, the next generation of breakthroughs for our greatest healthcare needs will never materialize. Nor will the jobs to produce them. Commissioner Hamburg has called the FDA "America's Innovation Agency," which might be considered more an aspiration than historical fact.[13] But it is an aspiration we share, and believe that PDUFA V will be an important step in accomplishing it.

13 Margaret Hamburg, "America's Innovation Agency: The FDA," *Wall Street Journal*, August 1, 2011.

APPENDIX

Coinciding with PDUFA V, Congress is considering additional legislative approaches to speeding drug approvals.

- **The Faster Access to Specialized Treatments (FAST) Act**. Introduced by Reps. Stearns (R-FL) and Towns (D-NY), FAST puts into law an "accelerated approval" pathway for drugs that are in clinical trials with FDA targeting serious and life-threatening diseases that lack current treatments. Among other things, the bill would enable drug sponsors to request fast-track designation by the FDA. It would also offer greater flexibility in designing clinical trials involving rare disorders. Portions of the FAST Act are included in the House's draft version of PDUFA V.
- **The Transforming the Regulatory Environment to Accelerate Access to Treatments (TREAT) Act**. Introduced in the Senate by Sen. Kay Hagan (D-NC). Similar to FAST, this bill focuses on regulatory innovation in areas such as the accelerated approval and fast-track processes to speed the development of therapies for patients with serious or life-threatening diseases. It focuses on unmet medical needs, significantly advancing the standard of care, and targeted therapies for serious or life-threatening diseases.
- **The Advancing Breakthrough Therapies for Patients Act**. Co-sponsored by Sens. Michael Bennet (D-CO), Orrin Hatch (R-UT), and Richard Burr (R-NC), the bill would create a flexible pathway for the FDA to evaluate products to "treat serious or life threatening disease or conditions" when preliminary clinical evidence "indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints." In addition, the legislation encourages the FDA to ensure that clinical trial designs are as efficient as possible. It sets deadlines for draft and final guidance for sponsors on how to seek breakthrough, accelerated approval, and/or fast track designation. And there is a requirement the Secretary of HHS to commission an independent entity, within four years, to evaluate the "quality, efficiency, and predictability" of the FDA's compliance with the legislation.

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