COMPETITIVENESS AND REGULATION:
THE FDA AND THE FUTURE OF AMERICA'S BIOMEDICAL INDUSTRY

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INTRODUCTORY LETTER

This is a report about the relationship between FDA regulation and the competitiveness of the U.S. biopharmaceutical and medical technology industry. Since the invention of biotechnology in California in the 1970s, America has emerged as the global leader in biomedical innovation. What fueled this growth was an extraordinary public-private partnership, beginning with the National Institutes of Health (NIH), whose funding for basic research laid the scientific foundations for countless breakthroughs in drugs and medical devices. Basic research by itself, of course, was not enough. Developing and manufacturing products for patients required massive amounts of private investment, backed by investors willing to assume the risk that accompanies leading-edge science. Overall this partnership has produced great benefits, both for the American economy and for patients everywhere.

Beyond the relationship between the NIH and the private sector in discovery, though, there has been another critically important partnership between industry and government centered at the FDA. For when it comes to new drugs and devices, the Agency is the gatekeeper, deciding which products may enter the market, and under what conditions. This is an enormously powerful, often underappreciated, role, with great implications for the economy and for public health.

The data presented here — gathered and analyzed by Simon Goodall and his team at the Boston Consulting Group — clearly indicate that today's FDA is not keeping pace with U.S. biomedical innovation. The Agency-industry partnership is strained by unexplained regulatory delays, by a lack of clear standards for what clinical data are

David Gollaher, PhD

necessary for product approval, and by a bureaucracy whose communications are neither consistent nor predictable.

The result of uneven performance at the Agency has been to increase the risk associated with regulation, dampening investment in companies whose products face FDA regulation. Meanwhile, as global competition in high-tech industries has intensified, other nations have adapted their regulatory systems to out-compete the FDA. The flight of medical technology product launches to EU countries should be a serious cause for concern for policymakers and patient advocates alike.

If the industry-FDA partnership is troubled, however, now is the time to repair it. With Congress and the Obama Administration focused on competitiveness and job creation, along with reducing the burdens of regulation, and with industry user fees up for reauthorization, it is the perfect time to reengineer the FDA for the 21st century.

David Gollaher, PhD
President and CEO
California Healthcare Institute

EXECUTIVE SUMMARY

Over the past generation, American scientists and entrepreneurs have produced a steady stream of biomedical breakthroughs that have saved and improved billions of lives around the world. Along the way, they built a global drug and device industry that became a powerful engine of prosperity, generating hundreds of thousands of high-wage jobs and enhancing the health of the U.S. economy.

In recent years, however, as evidence in this report makes clear, the environment for medical innovation has deteriorated. This is partly the result of the financial crisis and ensuing Great Recession, which sharply reduced investment capital. But the most critical factor has been the Food and Drug Administration (FDA or Agency). For the Agency's policies and activities exemplify President Obama's critique of a regulatory system whose "rules have gotten out of balance, placing unreasonable burdens on business — burdens that have stifled innovation and have had a chilling effect on growth and jobs."[1]

Striking the right balance between protecting patients, on the one hand, and ensuring that beneficial and life-saving innovations get to market as soon as possible, on the other, is at the heart of the FDA's mission. And 2011-2012 is a pivotal time for Congress and the Administration to assess the Agency's performance. Over the next 18 months, Congress will consider reauthorization of the user fee programs for biopharmaceuticals and medical devices. The Prescription Drug User Fee Act (PDUFA) and subsequent Medical Device User Fee and Modernization Act (MDUFMA), originally enacted in 1992 and 2003, were designed to provide more resources for the Agency. In turn, the legislation also spelled out improved performance standards and timelines for FDA reviews.

After periods of improvement, though, beginning in 2007 FDA performance has slipped. From the average of the previous PDUFA and MDUFMA rounds of 2003-2007 to today, drug and biologics review times have increased 28 percent, device 510(k) clearances have slowed by 43 percent and PMA device reviews are taking 75 percent longer. Contributing factors include new demands and responsibilities Congress assigned to the Agency as part of PDUFA IV and the FDA Amendments Act of 2007. At the same time, several high-profile safety problems with drugs and devices brought intense pressure on the FDA from Congress, the press and consumer advocates. The Agency's reaction was to focus less on the benefits of new products than on potential risks and to try to mitigate risk by demanding larger, more extensive (and more costly) clinical studies. From industry's perspective, in the words of a top FDA official, the regulatory process has become increasingly "unpredictable, inconsistent and opaque."[2]

Meanwhile, outside the United States, other nations have engaged in what might be called regulatory competition. The mid-2000s saw concerted efforts to increase the efficiency and elevate the stature of foreign regulatory agencies. Most prominently, European Union (EU) drug and device regulators

[1] Obama, Barack. Editorial: Toward a 21st-Century Regulatory System. *Wall Street Journal*, Jan. 18, 2011.

[2] Shuren J. Cover letter to proposed reforms: A Letter from the Center Director. FDA CDER. Jan. 19, 2011. (Dr. Shuren referred to the 510(k) approval process for medical devices, but his comment applies equally well to biopharmaceuticals.)

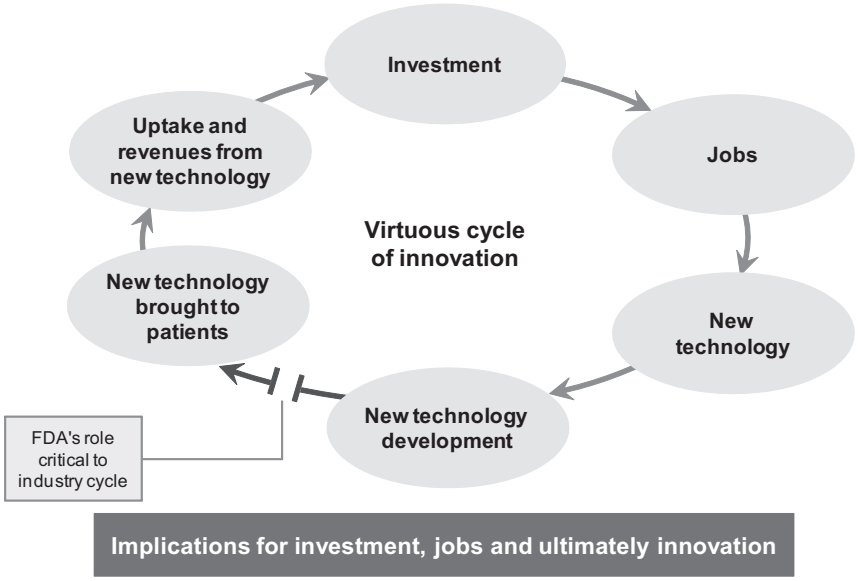
understood that streamlining their approval processes could be a strategy to attract business. In consequence, the past decade has seen a dramatic shift in clinical trials and product launches by U.S. firms to Europe. As global competition has risen, inefficiency at the FDA has resulted in American inventions being made available to patients and physicians in other countries first. This also has pushed jobs and revenues offshore, helping other nations gain experience in building infrastructure and scaling up new biopharmaceutical and medical technology products. Such capabilities and expertise are critical components in perpetuating the cycle of innovation, as well.

Twenty years ago, Congress recognized a "drug lag" between the United States and Europe and worked with industry to reinvigorate the FDA. This was the genesis of industry user fees. Today's competitive landscape is more complex, and the implications of FDA inefficiency are far greater. So it is imperative that legislators, the Agency, industry leaders and patient advocates agree on a practical plan to enable the FDA to function as smoothly and efficiently as possible.

With PDUFA and MDUFMA due for renewal in 2012, Congress must focus on the FDA's mission, on the optimum balance between benefits and risks, and on the direct and indirect costs regulation imposes on public health, biomedical innovation, the economy, job creation and American competitiveness. The reauthorization process also opens an opportunity to evaluate and correct any provisions in past user fee legislation that detract from the FDA's performance.

Industry is committed to strengthening its partnership with Congress and the Agency. Positive policy and operational improvements at the FDA, along with constructive legislation, will encourage biopharmaceutical and device innovation. Indeed a strong, science-based Agency and an efficient, predictable and transparent regulatory process are essential elements of the biomedical innovation ecosystem. And working together, Congress, the Agency, industry and other stakeholders can maintain the high standards of safety and effectiveness that doctors, patients and their families expect while also strengthening the biomedical sector's ability to attract the investment essential to secure U.S. global leadership in life sciences.

Consequences of Slow Regulatory Process on Innovation Cycle.



COMPETITIVENESS AND REGULATION:
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INTRODUCTION

The U.S. Food and Drug Administration (FDA or the Agency) directly regulates products and activities that account for one-fifth of the U.S. economy. The FDA's scope is vast. It encompasses everything from chickens to eggs; from cosmetics to tobacco; from the simplest medical devices, like tongue depressors and bandages, to the most advanced technologies, such as artificial hearts or cancer-treating monoclonal antibodies. Its mission is to protect and improve public health, and Agency officials underscore that this charge also includes advancing biomedical innovation.[3] (See Appendix A for background on the FDA.)

Because FDA approval is required before biopharmaceutical, medical device and diagnostic products can go to market, the Agency's policies and actions shape the environment for research and development. Companies and investors rely on an efficient, well-articulated and predictable regulatory process in order to make informed decisions. To raise capital and to hire workers, businesses need confidence in their ability to navigate the marketplace and the regulatory system.

The U.S. economy has benefited from predictable regulation. From 1980 through 2008 (the most recent full year for which comparative data is available), the life science industry's job creation was spectacular, contributing to economic growth across the country. In 2008, approximately 655,000 Americans were directly employed by the biopharmaceutical industry, and 423,000 others worked for medical technology companies. Salaries averaged $96,500 for biopharmaceutical workers and more than $58,000 for those in medical technology firms.[4,5]

As for the FDA, the Agency's policies and organizational structure have served as models for regulators in most industrialized and developing nations. The technical strength of the FDA and the clarity of its regulatory process helped the United States become the global leader in biopharmaceutical, medical device and diagnostic innovations.[6]

In the 21st century, however, the regulatory environment at the FDA has become troubled to a point of near crisis. Using extensive analyses of FDA data, company surveys and executive interviews, this study examines the decline of the Agency's performance and how its regulatory practices have become ambiguous, unpredictable and unnecessarily burdensome. Because the FDA does not operate in a vacuum, this report also explores the influence of external factors, such as the Great Recession, on industry's attitude toward regulation and how financial strains in today's market magnify regulatory risk.

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[3] Hamburg M. Speech: FDA and the American Public: The Safety of Foods and Medical Products in the Global Age. Delivered to Center for Strategic and International Studies, Washington, DC, Feb. 4, 2010.

[4] PhRMA. Fact sheet: The Biopharmaceutical Sector's Impact on the Economy of the United States. Published 2010. Accessed 01/19/11 at http://www.phrma.org/sites/phrma.org/files/PhRMA_U_S__Fact_Sheet_2008_vFINAL_2.pdf

[5] AdvaMed. Report: State Economic Impact of the Medical Technology Industry. June 7, 2010. Accessed 01/19/11 at http://www.advamed.org/NR/rdonlyres/F9FF4E5B-BD99-4245-A9F4-A6CA85A8896B/0/StateEconomicImpactoftheMedicalTechnologyIndustry61510.pdf

[6] Carpenter, Daniel. *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton, NJ: Princeton University, 2010.

Simply put, the FDA is the decisive gating factor in the biomedical investment and innovation ecosystem. Reversing present regulatory trends is essential to sustaining the U.S. biomedical industry as a vibrant source of technology jobs and encouraging future advances to improve public health.

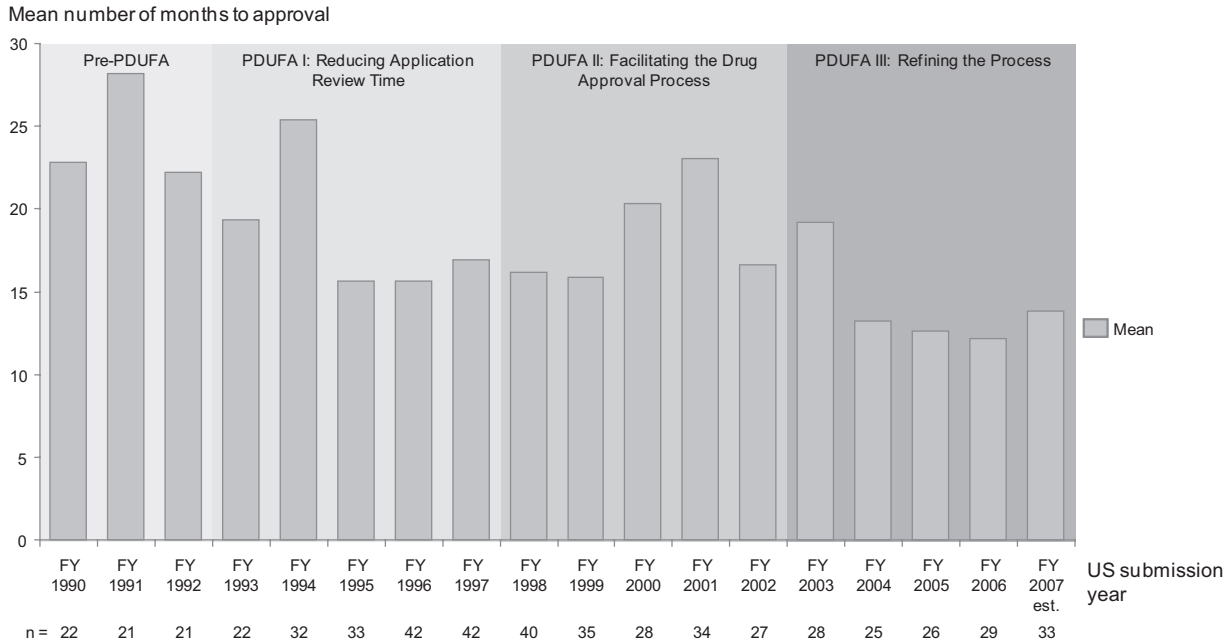
DRUG AND DEVICE REVIEW AT THE FDA: ORIGINS OF USER FEES

In the 1980s, the FDA required two and a half years — and sometimes up to eight years — to review new drug applications (NDAs). These delays generally reflected a lack of adequate resources to process the volume of submissions in a timely way. Policymakers and others recognized a growing "drug lag" in approval of new medicines in the United States versus elsewhere. In fact, by the early 1990s, fully 70 percent of new medicines were first approved overseas, with 60 percent available elsewhere for more than a year before being approved by the FDA.[7]

Prescription Drug User Fee Act

The tipping point was public anxiety in the late 1980s around the AIDS epidemic. This put the FDA in the spotlight, with patient advocates and the press pointing out the human costs of a protracted regulatory process. Lawmakers worked with industry and activists to secure more resources for the Agency and to streamline clinical trials. Together, Congress and industry developed legislation — the Prescription Drug User Fee Act (PDUFA) — that would enable companies to augment the Agency's funding by paying fees along with applications. Enacted in 1992, this statute required that the new fees (approximately $200,000 per application) be designated for hiring more reviewers. In addition, for the first time, the FDA committed to specific drug review performance standards. For example, for fiscal year 1994, Congress required the Agency to review and act upon 55 percent of NDAs within 12 months.

[7] U.S. Food and Drug Administration. Third Annual Performance Report: Prescription Drug User Fee Act of 1992, Fiscal Year 1995 Report to Congress. Dec. 1, 1995.



Source: BCG analysis of all NME and NBE submissions, modeling of time to approval for submissions in process. For methodology see details in the appendix. Database may not be complete for FY 2005-2007. When factoring in two missing submissions per year FY 2005-2007 and assuming that all are approved in FY 2011, mean time to approval would be: 2005 = 16 months, 2006 = 15, 2007 = 17

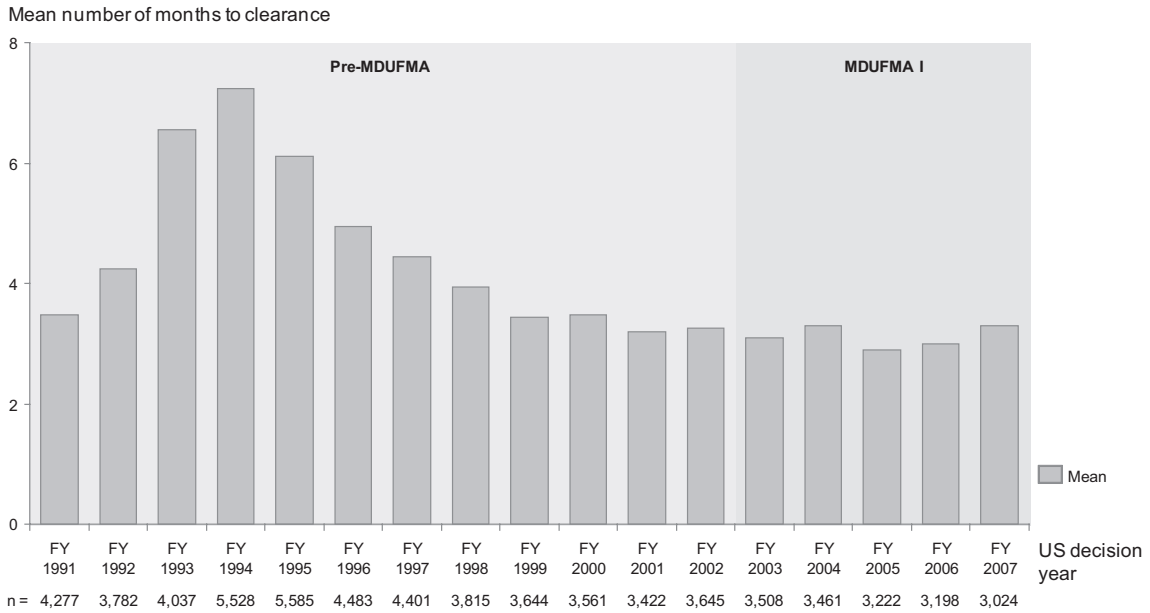
FIGURE 1. Three PDUFA Cycles 1993-2007.

There have been four consecutive PDUFA programs over the past 17 years; the current legislative authority for PDUFA IV, reauthorized in 2007 by the FDA Amendments Act, will expire in September 2012. As user fee legislation was reauthorized in 1997, 2002 and 2007, the Agency committed to review 90 percent of priority NDAs within six months, and 90 percent of standard NDAs within 10 months. As shown in Figure 1, each successive PDUFA reauthorization, from the 1990s through 2007, strongly correlates with improved review times and performance gains. (See Appendix B for more information on key provisions of each successive drug user fee act and Appendix C for notes on the methodology used to calculate the data presented here.)

Medical Device User Fee and Modernization Act

Despite occasional criticism, PDUFA has been widely considered a success. And after years of debate, the medical device industry and Congress created a similar program – the Medical Device User Fee and Modernization Act of 2002 (MDUFMA).

The main problem in formulating MDUFMA lay in the structure of the medical device industry and the fact that innovation in devices and drugs is quite different. Drugs work at the molecular level, altering complex biological systems that are only partially understood. Medical devices, such as implants, are technologies to enable or improve physical functions and, therefore, are easier to characterize and more predictable. The next generation of a medical device typically features improved materials or components, whereas an improved drug may be a new molecule that targets a different receptor or is combined with a second agent for greater effect. The gold standard for testing drugs is the randomized, controlled trial (RCT), in which matched cohorts of patients receive either an active medicine or a placebo. Such trials are difficult to do for medical devices and are seldom necessary to answer basic questions about whether a technology is safe and effective. (See Appendix B for



Note: Data cut by year of decision
Source: FDA device approval database; BCG analysis

FIGURE 2. 510(k) Clearances Leading Up To and Through MDUFMA I.

more information on medical device classification, approval processes and key successive medical device user fee act provisions.)

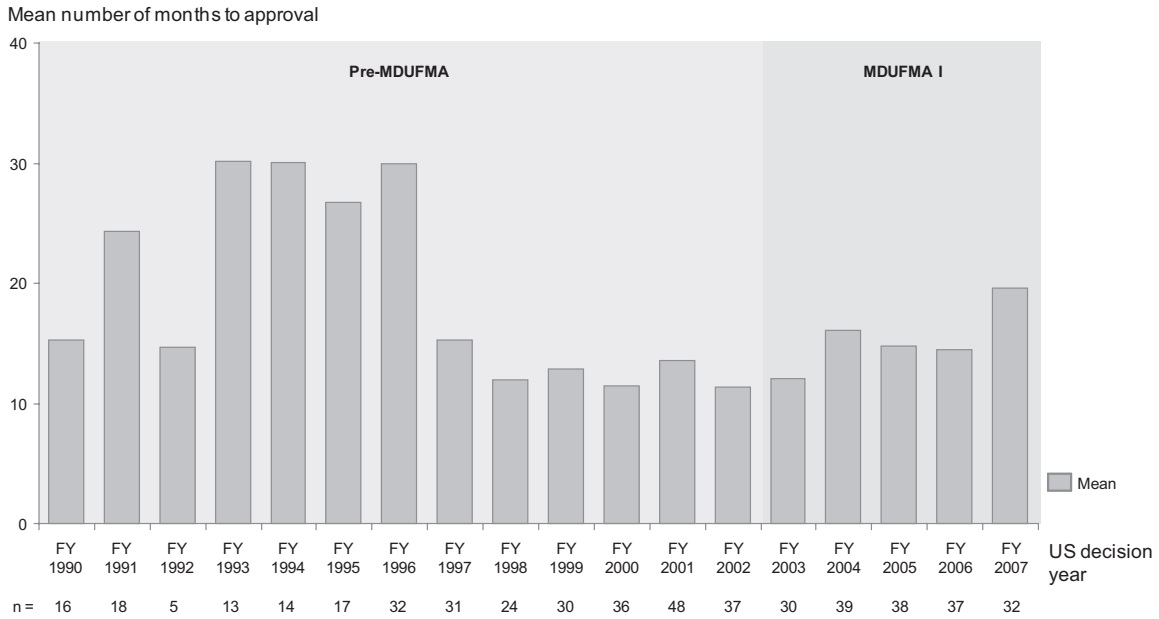
Similar to the drug user fee program, MDUFMA instituted industry user fees for the review of pre-market applications, reports, supplements and pre-market notification submissions. The idea was to provide additional resources to make FDA reviews more timely, predictable and transparent. MDUFMA fees helped FDA expand available expertise, modernized its information management systems, offered new review options and provided more guidance to prospective applicants. As with drugs, the goal was to clear safe and effective medical devices more rapidly, benefiting applicants, the healthcare community and patients.

The lag times with 510(k) and PMA clearances improved ahead of the enactment of MDUFMA (Figures 2 and 3), and the review times for these devices held generally steady from fiscal year 1999 into fiscal year 2007. In that year, Congress reauthorized the program with the Medical Device User Fee Amendments of 2007, which was itself part of a larger bill, the Food and Drug Administration Amendments Act of 2007 (FDAAA).

Current FDA Performance

If user fees led to demonstrable improvements in Agency performance, critics of user fees argued that they have made the FDA a captive of the industry it regulates. In fact, the Agency frequently has been under assault from the press, consumer groups and members of Congress for being too close to industry and for inadequately protecting the public from faulty drugs and devices. The Agency's product reviews, as a result, increasingly have focused less on the benefits of new drugs and devices and more on their possible risks.

Complicating matters further, Congress has greatly enlarged FDA's scope into new fields (e.g., tobacco) and added to its responsibilities and authority. Yet federal appropriations have failed to keep up with new mandates, forcing greater Agency reliance on industry-funded user fees.



Note: Data cut by year of decision; PMA approvals only includes original approvals, no supplements
Source: FDA device approval database; BCG analysis

FIGURE 3. PMA Approvals Leading Up To and Through MDUFMA I.

These increased responsibilities would be hard to manage even if science stood still. But, of course, it has not. The past decade has witnessed an explosion of knowledge, exemplified by the Human Genome Project, that has transformed drug and device innovation. Scientists today routinely employ high-throughput genetic sequencing to indentify targets for small-molecule drugs. And medical device makers are working on ways to integrate nanotechnology and wireless communications in leading-edge technologies. The accelerating rate of scientific and technological advances severely strains the FDA's ability to keep pace — and poses significant limits on the Agency's future responsiveness and performance.

Pharmaceutical and Biologics Sectors

Through its every-five-years review and reauthorization of PDUFA, Congress has significantly increased the FDA's responsibilities and allocated the increased costs to industry user fees. For instance, PDUFA III gave the FDA authority to use user fee resources on risk management and post market surveillance. Also added under PDUFA III came the codifying of best practices into "Good Review Practices" (GRPs). This action was intended to improve the review process by applying successful techniques across the Agency. Yet, as the FDA web site notes, "Since GRPs can change and evolve frequently as a result of new science, statutes, regulations, guidances and accumulated experience, the policies will be updated regularly." Further, "Review staff are expected to follow GRPs and may depart from them only with appropriate justification and supervisory concurrence."[8] The Agency has yet fully to implement GRPs, leaving the regulatory process in a state of transition.

For drug reviews, the Agency regularly draws on advisory committees composed of outside experts. Additional responsibilities implemented under FDAAA and PDUFA IV in 2007 gave advisory committees stronger authority to provide expert opinion on issues pertaining to trial design, safety and efficacy. The trouble is, though, PDUFA IV also imposed more stringent conflict-of-interest rules, potentially precluding some of the most knowledgeable and qualified medical specialists from serving on advisory committees.

Further, the Risk Evaluation and Mitigation Strategies (REMS) provisions, included under FDAAA, have codified many accepted risk management practices. REMS were intended to enable manufacturers to evaluate and mitigate serious risks associated with the use of an otherwise beneficial drug and to demonstrate that the drug's benefits outweigh its risks. Drugs are, after all, approved on the basis of clinical studies involving limited numbers of patients. When these drugs are used by thousands or millions of patients in the general population over longer periods, new problems may surface. Based on further post-launch analysis, the Agency reasoned that it could approve products that it might otherwise deem too risky. The implementation of REMS, however, has had almost the opposite effect. Negotiating with the Agency on REMS requirements has stretched review times and lengthened FDA's review processes. In response, industry has proposed standardizing the REMS process by developing a single platform for certain REMS programs instead of designing a unique program for each drug.[9]

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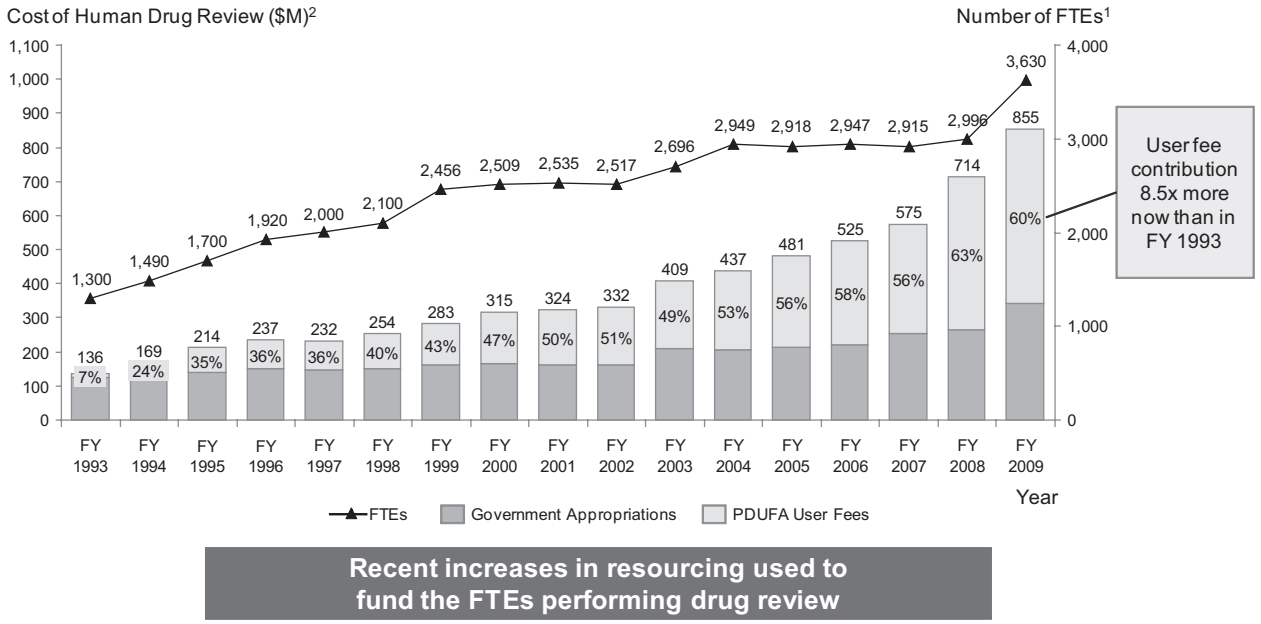
[8] U.S. Food and Drug Administration. Web page: Good Review Practices (GRPs). Accessed 01/03/11 at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm118777.htm.

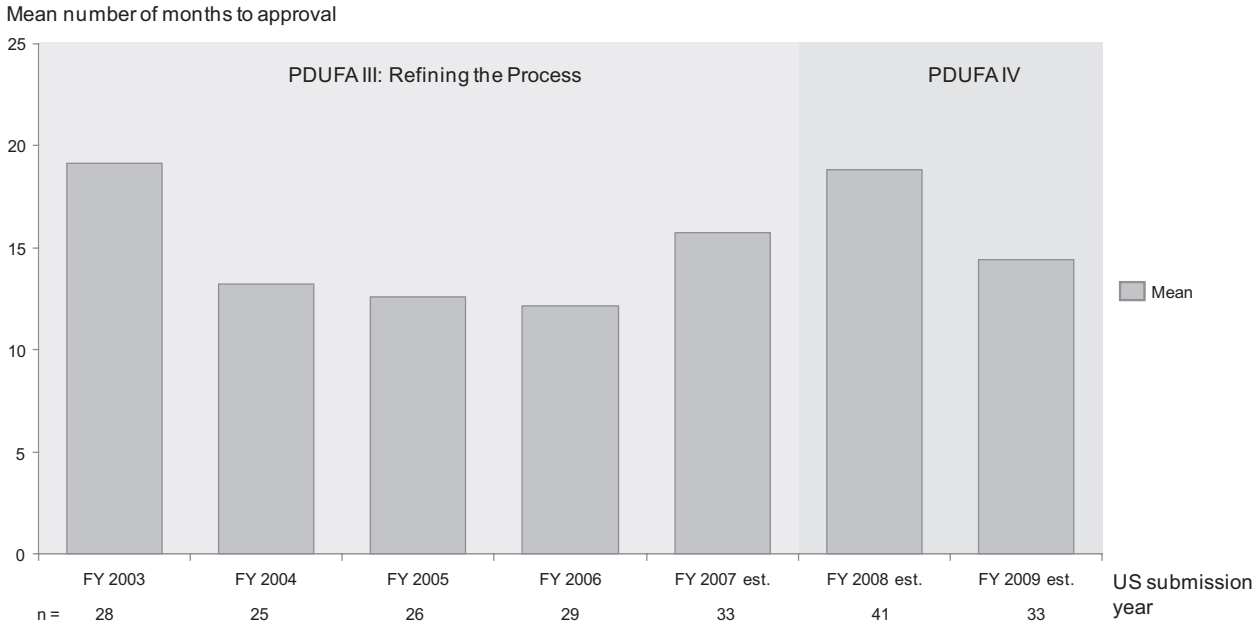
[9] Moscovitch B. Brands, Generics, Biosimilars User Fees Top 2011 FDA Drug Agenda. Posted 01/12/11 at HealthPolicyNewsStand.com.

With Congress reluctant to increase its baseline appropriations, over the course of each PDUFA reauthorization the FDA has become increasingly dependent on user fees to fund drug review. As Figure 4 demonstrates, today user fees account for 60 percent of the costs associated with FDA drug review — 8.5 times more than when user fees were first instituted — while until just recently, congressionally appropriated funding of the Agency was generally flat.



1. Total FTEs in Human Drug Review Program. Source: 1993-1999 from FDA White Paper: Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications; 2000-2009 from FDA Annual Budget All Purpose Table Human Drug Program Total FTEs. 2. Total Cost of Human Drug Review
Source: FDA PDUFA Annual Financial Reports, Total Cost of the Process for the Review of Human Drug Applications; BCG analysis

FIGURE 4. FDA's Growing Dependence on User Fees to Fund Drug Review.



Source: BCG analysis of all NME and NBE submissions, modeling of time to approval for submissions in process. For methodology see details in the appendix.

FIGURE 5. Drug Review Timelines Lengthened In 2008.

In the past, industry has accepted increased user fees and expanded Agency requirements when the fees have corresponded with improved review times. Beginning with PDUFA IV, however, added requirements and responsibilities have correlated with longer FDA drug review timelines and growing frustration within industry. As Figure 5 illustrates, the PDUFA IV class of 2008 saw an average approval time of 18.9 months for a 28 percent increase over the average PDUFA III time of 14.7 months.

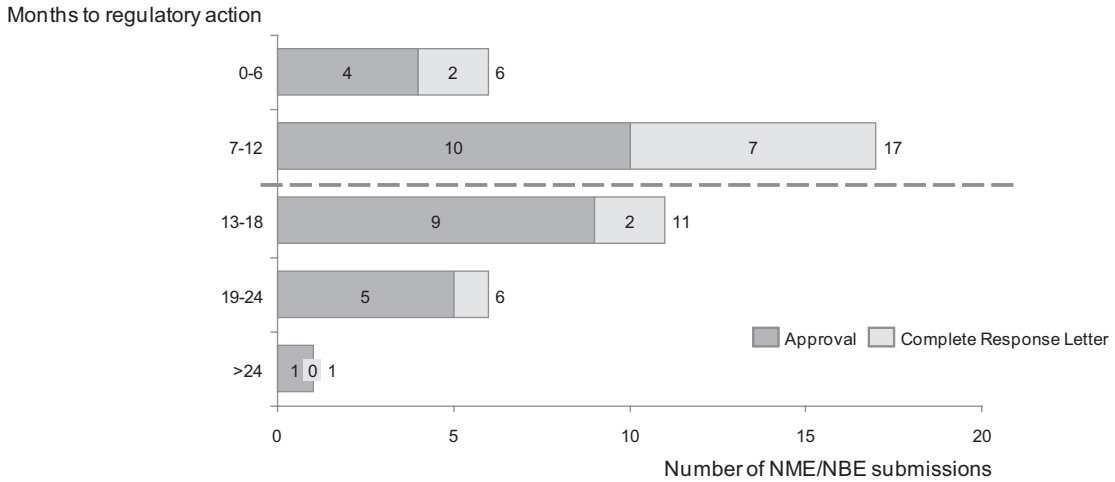
In 2009, the average approval time of 14.5 months did represent a 1.3 percent decrease from the average PDUFA III timelines. However, under PDUFA, the Agency's goal is to communicate regulatory action decisions within six months for priority applications and 10 months for standard applications, performance levels the FDA currently is not meeting.[10]

A closer look (Figure 6) at the new molecular entities (NMEs) and new biologic entities (NBEs) submitted to the FDA for approval in 2008 further illustrates the slowdown in approval times. Fully 45 percent of the year's class were in process for more than a year before regulatory action was taken.

Medical Technology Sectors

The FDA did not systematically regulate medical devices until 1976, and historically the Agency has been viewed as evaluating devices less rigorously than drugs. But devices work in different ways and, as Congress realized when it adopted the Device Amendments of 1976, devices required a different approach. Devices are typically products designed and engineered for a given use, not chemical compounds or biologics manufactured from living cells. Changing the molecular structure of a drug or biologic often changes the way it works in the body, so even minor modifications require new clinical trials. Devices, in contrast, may be altered in minor

[10] U.S. Food and Drug Administration. Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. April 2005.



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.

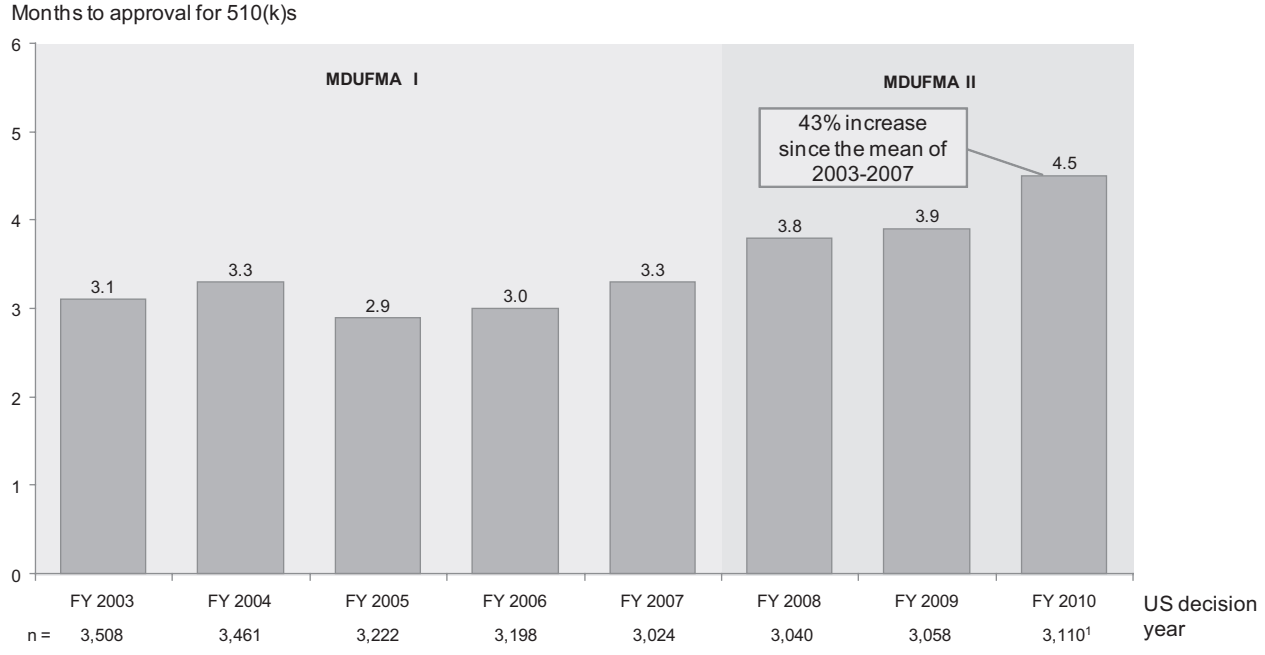
FIGURE 6. Status of NMEs/NBEs of 2008 Seeking FDA Approval.

ways — switching to a new metal alloy, installing a longer-lasting battery, using a better polymer — so that the effects on the product's safety and efficacy profile are predictable. Treating every modified version as though it were an entirely new device would discourage incremental improvements by making them prohibitively time-consuming and costly with scant benefit to the public health.

While the overall safety record of the U.S. medical technology industry is exemplary, between 2007 and 2010, as the device user fee act was being reauthorized, several product recalls and lawsuits raised concerns that the FDA had gotten too close to industry and had failed to keep unsafe devices off the market. Criticism of the Center for Devices and Radiological Health (CDRH), the FDA branch responsible for approving medical devices, boils down to two contentions. The first is that the 510(k) exemption process is too liberal, and the second is that the PMA review process should be stricter.

Criticisms of the FDA's review of devices — from consumer groups, Congress and from within the Agency itself — have led to turmoil in the medical technology approval process. Indeed, survey research among industry executives suggests that the present performance of CDRH is at an historic low.[11] As shown in Figures 7 and 8, the past few years have seen significant slowdowns in clearance times, even as submissions are down from the early part of the decade. Complex PMA submittals saw review periods increase 75 percent over the MDUFMA I (2003-2007) average to 27 months in 2010. For 510(k) submissions, the approval time has increased 43 percent to an average of 4.5 months in fiscal year 2010 over the average of about three months under the MDUFMA I years of 2003-2007. Further, interviews with industry executives suggest

[11] Meer A and Makower J. Survey: FDA Impact on US Medical Technology Innovation. Stanford University, Palo Alto. November 2010.



1. 2010 number is pro-rated to obtain end of year numbers
Note: Data cut by year of decision; 510(k) approvals only includes original approvals, no supplements
Source: FDA device approval database; BCG analysis

FIGURE 7. 510(k) Review Times Have Increased Under MDUFMA II.

that in an increasing number of cases, the Agency is requiring more and more clinical data for 510(k) submissions. Costs of conducting clinical trials and uncertainty about how much data the FDA will need to approve a product have become key concerns for device manufacturers.

Significant Changes Critical in User Fee Renewals

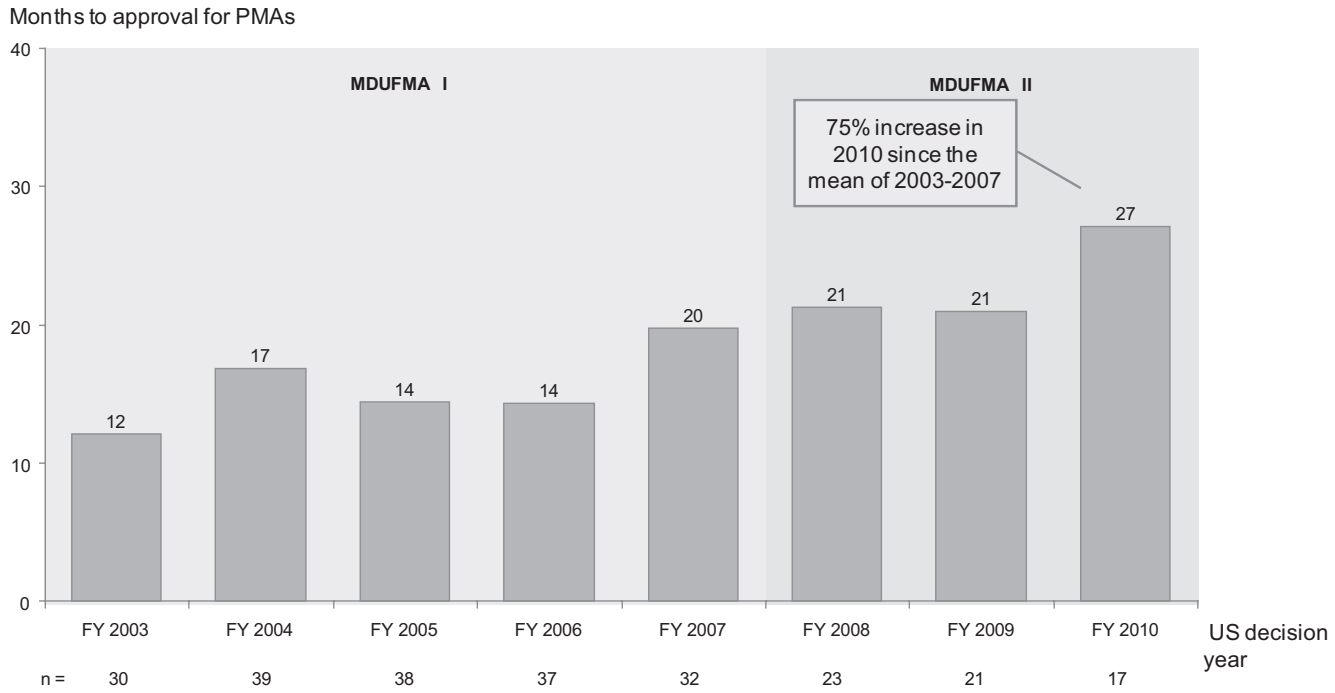
Delays in the FDA regulatory process (Figure 9) have alarmed the entire U.S. biomedical industry. For new drugs and biologics, average review times increased by more than four months (approximately 28 percent) in 2008 from 2003-2007. The 43 percent increase in 510(k) review times adds more than one month to the process. And for PMAs, the 75 percent increase translates to nearly a year longer.

As the FDA, industry, Congress and other stakeholders prepare for the next PDUFA and MDUFMA reauthorizations in 2012, these lengthening approval times are an important signal that the U.S. regulatory environment raises serious barriers to innovation. Before pursuing significant increases in user fees or expansive new authorities and requirements, Congress, the Agency and industry must first determine the source of the problem and develop practical solutions that will make the process more efficient. Resources are important, but simply increasing user fees will not address the underlying faults.

ENVIRONMENTAL FACTORS AFFECTING THE BIOMEDICAL INDUSTRY

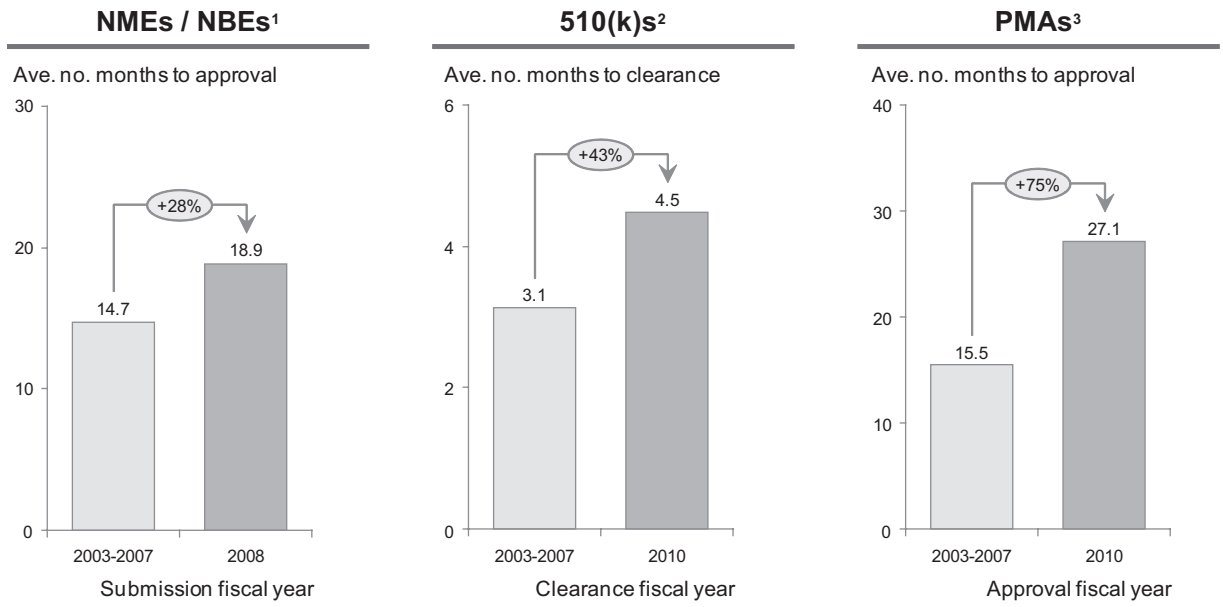
Impact of the Financial Crisis

The biopharmaceutical and medical technology industries operate in a global business system in which regulation is a basic factor. Coinciding with the slowdown at the FDA was the worst economic downturn since the Great Depression. And the



Note: Data cut by year of decision; PMA approvals only includes original approvals, no supplements, all AP* codes considered as aprovals
Source: FDA device approval database; BCG analysis

FIGURE 8. PMA Review Times Also Have Lengthened in Past Three Years.



1. NMEs and NBEs only, by fiscal year of submission date. given long cycle times for drug approval 2008 includes estimated figures for applications in process.
Source: Drugs@FDA; EvaluatePharma.
2. By fiscal year of clearance date. given shorter cycle times 510(k)s clearances only includes original clearances. Source: FDA devices database
3. By fiscal year of approval date, given relatively shorter cycles and lack of data on submissions in process. PMA approvals only includes original approvals. Source: FDA devices database

FIGURE 9. Review Times Have Increased Across All New Drug and Device Applications.

financial crisis of 2007-2008 had a dramatic and immediate effect on the financial condition and strategic initiatives of companies and industries around the world.

The biomedical industry is especially sensitive to the broader trends and flows of capital in the global financial markets. The Great Recession sharply changed the investment environment, especially the way investments flow to new ventures and early stage companies. Outlining these changes helps explain why, far more than in the past, the risks posed by drug and device regulation have become so important.

Much of the life sciences industry, including global biotech leaders like Amgen and Genentech, began as small startups funded by venture capital. And today, the vast majority of life sciences firms are small enterprises, many of whom rely on fresh rounds of venture investment to sustain operations. They typically have no product yet on the market or have one or two products commercialized that are yet unprofitable. In fact, the biotech sector as a whole reached profitability for the first time in 2009.[12]

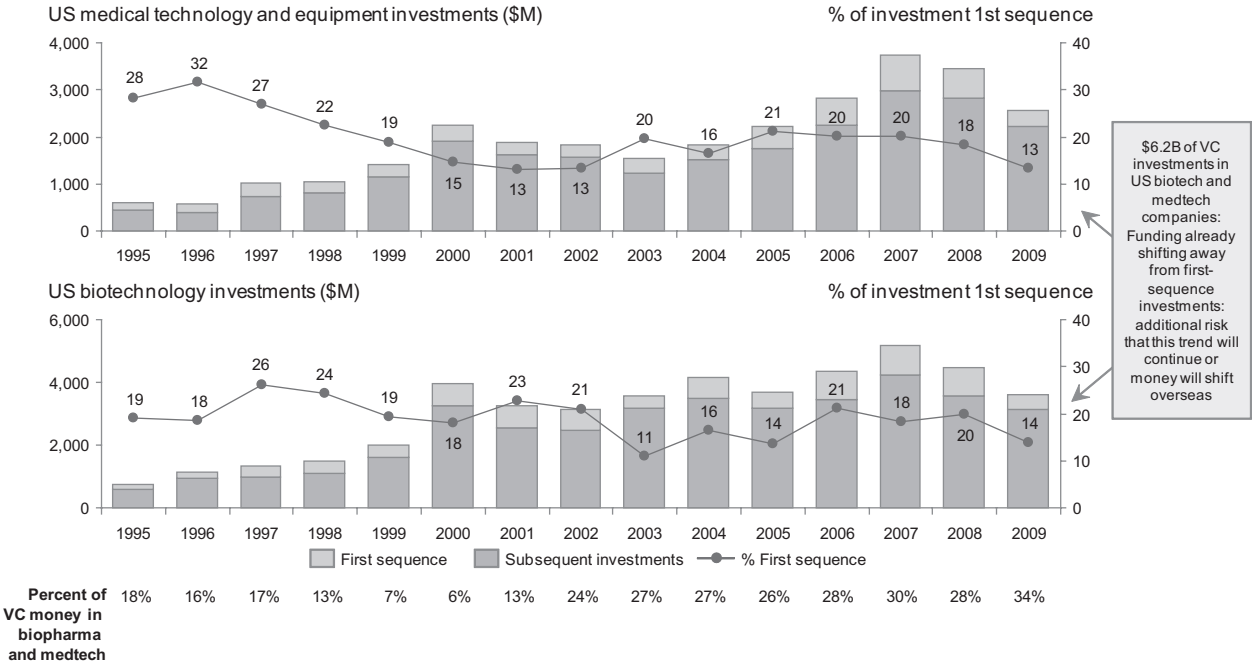
The global financial meltdown of 2008 devastated investment portfolios, including the pension funds and institutional endowments that historically have been the main source of venture capital. After the crash there was a cascade effect. A university endowment, for example, that historically allocated 10 percent of its portfolio for venture investments suddenly lost one-third of its value. So, even if it maintained the normal percentage, its allocation to venture would have dropped by one-third. But reaction to the financial crisis was to squeeze risk out of portfolios, and many institutional investors cut their venture allocations severely. As a result, many venture capitalists found themselves unable to raise new funds.

[12] Ernst & Young. Beyond Borders: Global Biotechnology Report 2010. Accessed 01/19/11 at http://www.ey.com/Publication/vwLUAssets/Beyond_borders_2010/$File/Beyond_borders_2010.pdf.

Meanwhile, venture firms themselves also sought to reduce risk. With capital scarce, their strategy is to reserve cash for their strongest portfolio companies — ones with proven products and clear paths to market. In 2010, venture capitalist investments in U.S. biotech and medical technology totaled $6 billion.[13] Yet the trend away from early-stage investments — ones that combine the greatest innovation with the greatest risk — continues (Figure 10). To make matters worse, the initial pubic offering (IPO) market for biotechnology and medical device companies all but vanished. After the collapse of iconic firms, Wall Street had little interest in offerings from young companies with no operating revenues that would need continuing infusions of capital over many years. Since 2008, public investments in biomedical companies have mainly gone to larger, established, publicly traded companies.

With capital hard to raise and little hope of going public, companies have adapted by redesigning their biomedical business model. For biotechnology, this has meant turning to large pharmaceutical firms. To raise capital for research and development, biotechnology companies are providing contract research, out-licensing their discoveries or selling late-stage development candidates as well as project teams or the whole company. For medical device firms, the new model generally entails grooming themselves to be acquisition candidates for global medical technology companies, which rely on acquisitions for growth. These symbiotic relationships between large and small companies are becoming the new normal.

[13] PricewaterhouseCoopers, *MoneyTree Report*, January 2011.



Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree™ Report, Data: Thomson Reuters

FIGURE 10. Investors Reducing Early Investments in Drug and Device Companies.

Regulatory Risk: Spotlight on the FDA

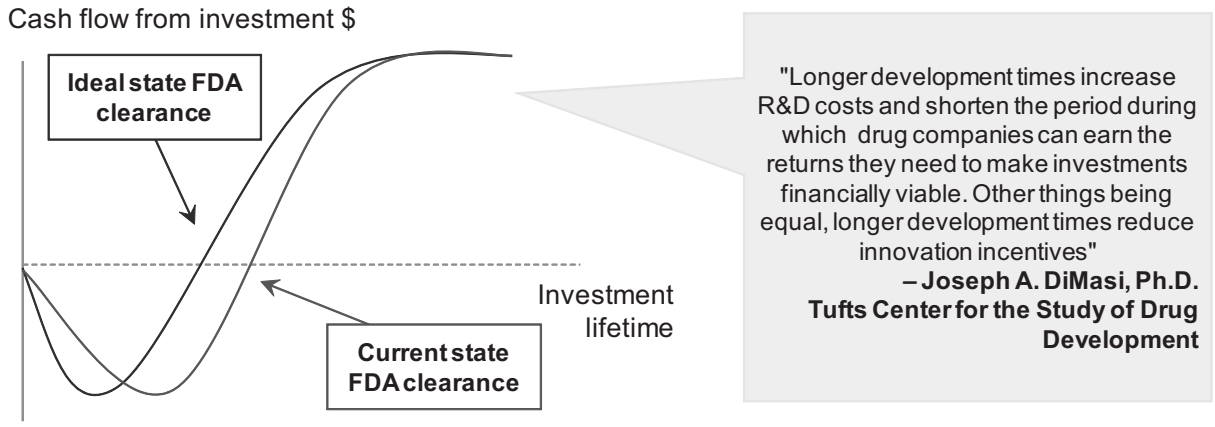
From investors' perspective, regulation has always been a risk factor. Products fail even in the best of circumstances. In a capital-constrained world, however, regulatory risk increases exponentially. Today the problem is that, for drugs and devices alike, clinical trial protocols change and data requirements expand without warning. Different reviewers in the same division apply diverse standards, and FDA personnel changes may add months or years to the review process. Among industry executives, unpredictability is viewed as a more serious problem than long review times. For a slow but predictable process would at least allow companies to plan and budget resources and communicate development timelines to doctors, patients and investors.

Unpredictability also figures into the strategy of companies that intend to be acquired. What becomes paramount to them is to pass an acceptable regulatory hurdle, launch in a major market, and demonstrate product adoption by physicians, patients and payers. Having passed these regulatory and market tests, a firm can present itself to potential acquirers as a lower-risk investment. Moreover, the acquiring company can value the startup enterprise based on its own business model, its regulatory expertise in other countries, its sales force and channels to doctors, hospitals and patients. From an investor's perspective, winning approval sooner in any market becomes far more valuable than gaining FDA and U.S. approval later.

Meanwhile, inefficiencies at the FDA cause companies to create mirror inefficiencies of their own. Costs for regulatory affairs staffs and consultants, for example, are growing to the point where they are nearing and, in some cases, exceeding spending for R&D in smaller biomedical companies.[14]

Nor are companies with products in the later stages of the product development process immune to the effects of lengthened reviews. Even established firms are less able to predict cash flow and therefore

[14] Meer A and Makower J. Survey: FDA Impact on US Medical Technology Innovation. Stanford University, Palo Alto. November 2010.



Source: "What's Time Got To Do With It?" http://content.healthaffairs.org/cgi/content/full/25/4/1188 (2006)

FIGURE 11. Delayed FDA Timelines Decrease Returns on Investment.

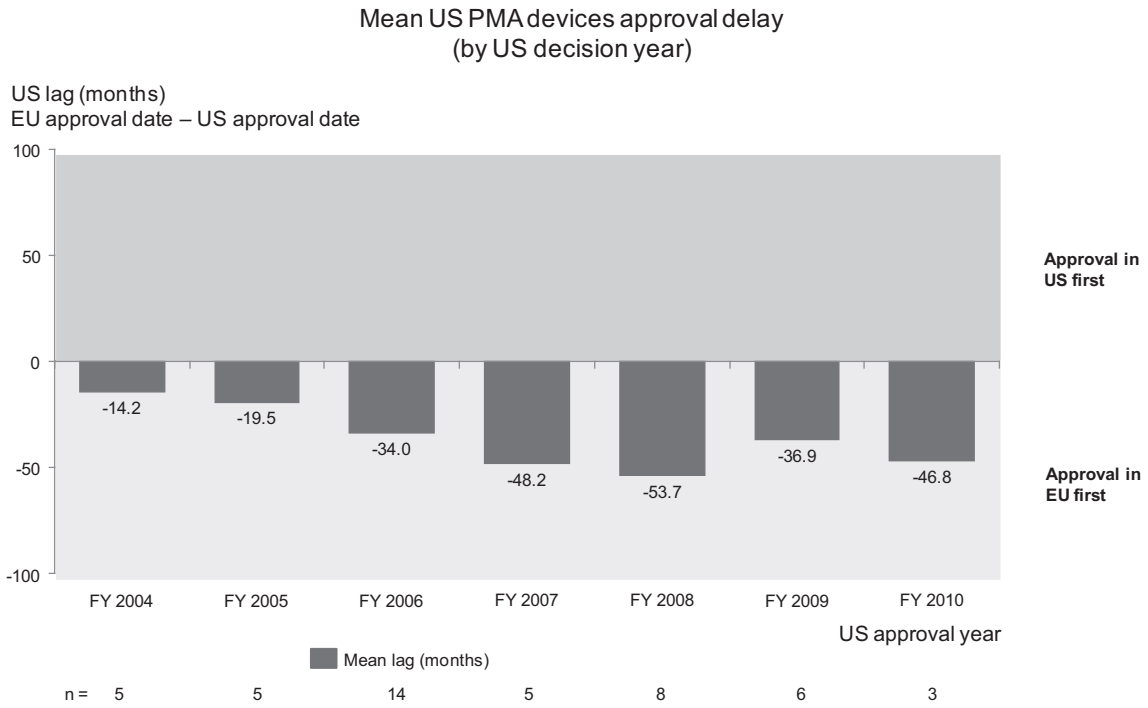
are less confident in maintaining staffing levels or ramping up for product launches or new development programs. In addition, delays in product approval may require the companies to set higher margins on their products to compensate. Given the limited patent protection periods on life sciences products, delays in approval decrease the period in which an innovator can generate returns on its investments (Figure 11).

Thus the recent capital crisis sharply increased regulatory risk or uncertainty. And levels of regulatory uncertainty — delays, missed timelines, doubts about eventual approval — that had been uncomfortable in good economic times became intolerable after the crash. Especially because, as investors and corporate executives came to realize, there are practical, alternative routes to bring products to market.

Biomedical Product Approval in the European Union

Before the formation of the European Union in 1993, clinical trials and drug applications had to be customized from country to country across the continent. European policymakers recognized that their separate sovereignties posed a serious barrier to growing the EU biopharmaceutical industry. Implementation of the EU opened the way for a single, unified regulatory regime that consolidated drug registration across Europe. At the same time, the EU's 27 member states, taken together, represent the largest market for drugs and devices in the world.

It is ironic that the EU drug regulatory system — the European Medicines Agency (EMA) — began by emulating the FDA's NDA policies and procedures, but recognized earlier and more clearly than the FDA just how fundamentally regulation



Note: Represents original PMAs
Source: Data compiled from all PMAs approved in the US for 12 different medical device companies, where total sample size n = 46; BCG analysis

FIGURE 12. Earlier PMA Device Approval in the EU Is a Standing Pattern.

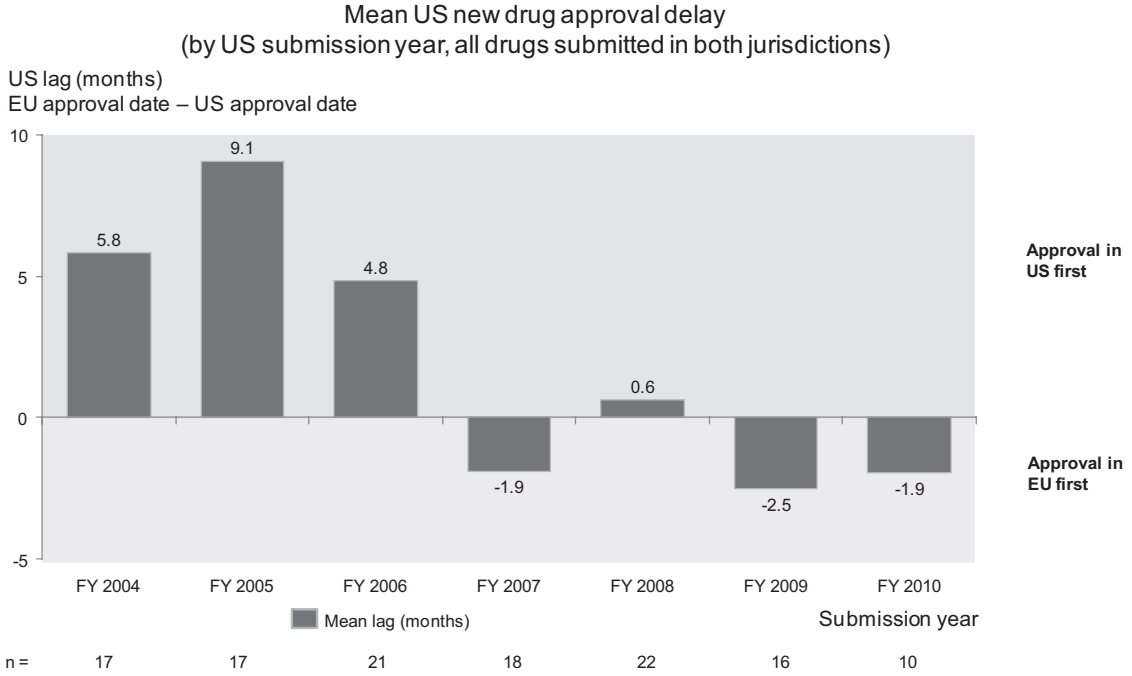
shapes investment and industrial growth. More specifically, the EMA saw how much Europe stood to gain by improving on the process that existed in the United States.

At the heart of the pan-European system of regulation, originated in 1995, were two core principles: consistency and timeliness. A consistent and transparent path to approval enables the EU's regulatory agencies to deliver on their 210-day time limit for new drug application reviews and the 90-day limit for Class III medical devices.

Pharmaceutical, biologics, medical device and diagnostics companies the world over have capitalized on the EU's philosophy. For complex medical devices evaluated via PMA in the United States (Figure 12), the EU system has consistently offered a faster route to market. However, recent years have witnessed a worsening of the lag, with such products being approved in Europe nearly four years ahead of the United States, up from just over a year earlier this decade.

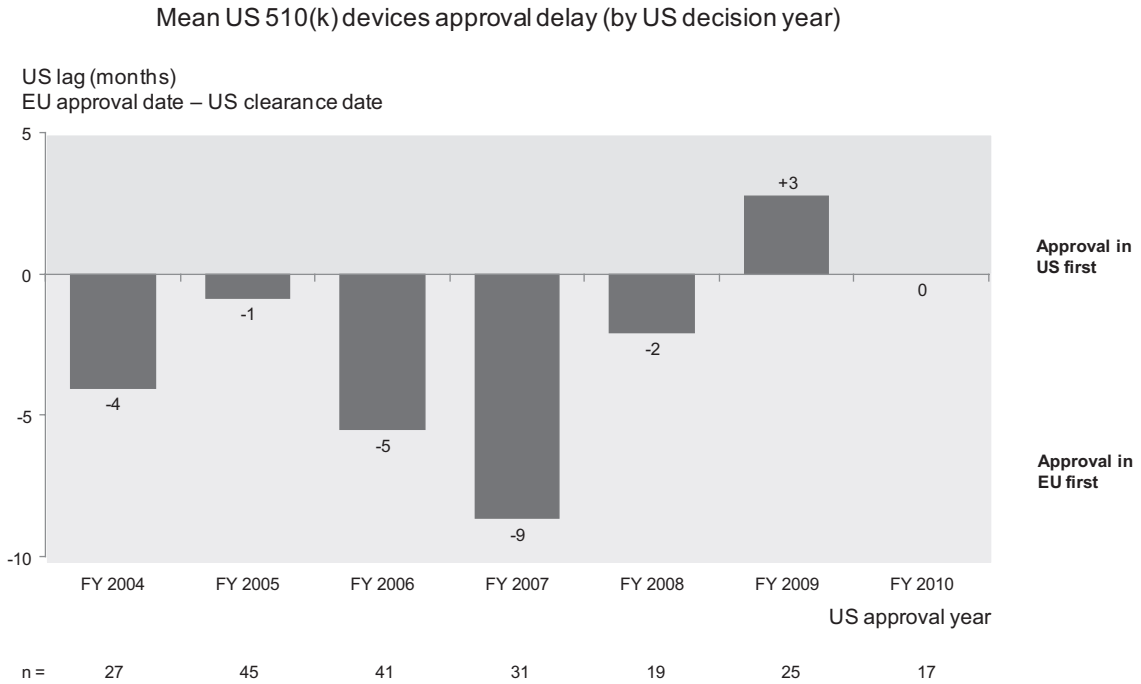
Since 2007, there has been a significant rise in the number of drugs approved in the EU first (Figure 13). Further, where new medicines were approved first in the United States by an average of nearly seven months between 2004 and 2006, the trend changed rather dramatically in 2007. That year, drugs were approved two months faster in the EU. Recent years show some evidence of a new "drug lag" with products approved on average two and a half months earlier in the EU than in the United States.

For most 510(k) devices, which seldom require clinical trials to gain approval, comparisons seem, at first glance, less clear (Figure 14). But the picture changes when one factors in products' level



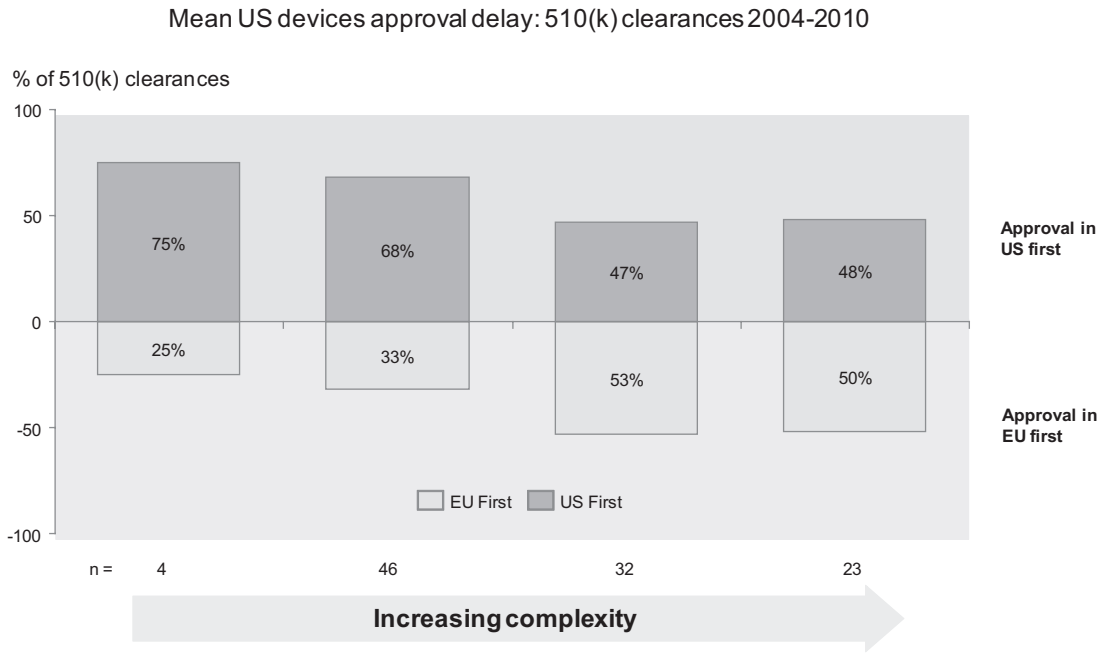
Note: Sample comprises only drugs being reviewed in both the US and EU, data are categorized by US submission year. Where drug has not been approved in one jurisdiction delay is counted as difference between first approval and 1/23/2011, Difference between 2004-2006 and 2007-2009 found to be statistically significant at the 5% significance level. See methodology for more information
Source: FDA drug database; EMA drug database; BCG analysis

FIGURE 13. Significant Change in Drug Approvals in U.S. and EU Since 2007.



Note: Represents original 510(k) application without clinical trials. Difference between 2004-2006 and 2007-2009 found to be statistically significant at the 5% significance level for probability of approval in US first, but not significantly for the mean lags. See methodology for more information
Source: Data compiled from 12 different medical device companies, where total sample size n = 205; BCG analysis

FIGURE 14. U.S. Approval Times for 510(k) Devices.



Note: Represents original 510(k) applications without clinical data. Devices classified using EU standard I-IIa-IIB-III where classification I is least risky while Class III is most risky i
Source: Data collected from 10 different medical device companies, where total sample size n = 205 data based on 105 devices for which EU classification was available

FIGURE 15. More Complex Devices May Be More Likely to Be Approved in EU First.

of complexity (Figure 15). From this perspective, there is a clear trend that the more complex, and often cutting edge, a product is, the more likely it is to be approved first in Europe versus the United States.

IMPLICATIONS

Because EU and U.S. regulators generally review identical drugs and devices — and, for drugs, often the same clinical trials data — it is fairly easy to compare and contrast their decisions and decision making processes. In that comparison for 510(k) devices, for example, recent research indicates that safety — as measured by the percentage of approved products recalled — has been a relatively minor issue.[15,16,17] More recently, a study by the Boston Consulting Group examined the rate of safety recalls for medical devices in Europe from 2005-2009 and compared them with the level of similar recalls in the U.S. The study focused on those products recalled because of significant health risks and found an average recall rate in Europe of 21 per year, compared to the tens of thousands of devices on the market. This is almost identical to the rate of equivalent recalls in the U.S.[18] As for timelines, especially since 2007, the FDA clearly has had a more cumbersome and unpredictable approval process. And companies are electing to work first with the regulatory body whose process is most transparent and likely to get their products to physicians and patients soonest.

The EMA has been forthcoming about its ambitions to encourage and facilitate innovation and research in the EU. In a number of high level meetings and documents, European drug regulators and other leaders have cited the pharmaceutical and healthcare biotechnology sectors as pillars of the EU's knowledge economy. Forward-looking goals outlined in *The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future*, for example, were designed, among other objectives, to encourage and facilitate innovation and research in the EU. In fact, the EMA has stated that its "role in enabling the pharmaceutical industry to achieve the objective of industrial competitiveness is crucial."[19]

The globalization of science, people and capital is accelerating. As organizations become adept and then expert at conducting research and development, clinical trials and business globally, their comfort with regulators around the world grows.

Regulation and American Competitiveness

Until the late 1990s, among the industrialized democracies, the FDA held something like a monopoly position. The Agency enjoyed more resources and tended to have deeper scientific expertise than regulators elsewhere. Obviously, companies make decisions about where to locate R&D, where to conduct clinical trials, where to launch new products and where to scale up manufacturing based on several factors. But it is evident

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[15] Hall R. Using Recall Data to Assess the 510(k) Process. Accessed 01/13/11 at http://www.iom.edu/~/media/Files/Activity%20Files/PublicHealth/510kProcess/2010-JUL-28/06%20Hall.pdf.

[16] Maisel W. "Premarket Notification: Analysis of FDA Recall Data." Accessed 01/13/11 at http://www.iom.edu/~/media/Files/Activity%20Files/PublicHealth/510kProcess/2010-JUL-28/05%20Maisel.pdf.

[17] Battelle. 510(k) Premarket Notification Evaluation. Accessed 01/13/11 at http://www.advamed.org/NR/rdonlyres/255F9405-677D-45B1-BAC8-0D4FD5017054/0/510kPremarketNotificationEvaluation.pdf.

[18] David S, Gilbertson E and Goodall S. *EU Medical Device Safety Assessment: A Comparative Analysis of Medical Device Recalls 2005-2009*. Boston Consulting Group, January 2011.

[19] European Medicines Agency. The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future. London, March 4, 2005. Accessed on 01/13/11 at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/10/WC500004903.pdf.

that these decisions are increasingly influenced by international differences in drug and device regulation. And in this age of globalization, firms can pursue research, development, clinical trials, early-stage commercialization, scaling and manufacturing anywhere in the world — often for less money than in the United States.

When U.S. companies locate development activities offshore, foreign physicians and health professionals gain early clinical experience with new products. In the case of medical devices, which tend to be incrementally improved based on what happens in the clinic, there is a classic feedback loop. As technologies go from prototype to mass production, design details are modified as physicians and manufacturers figure out what works best for patients and learn how to produce products efficiently. There is no substitute for tinkering with an invention in the real world. Over time, this process builds the chain of experience essential to technological innovation. Thus an American company's decision to launch a novel device in Germany because the regulatory pathway there is faster and more predictable results in German surgeons and technicians learning the fine points of applying the technology first. And, of course, it also means that German patients benefit from U.S. innovation before Americans do.

As operations move overseas, they also take U.S. experts with them in advisory and managerial roles. Capitalizing on the technical and intellectual expertise newly deployed within their borders, other nations are building the infrastructure necessary to sustain their own life sciences industries — and to woo innovators to operate there instead.

This practice of using regulation as a competitive tool is hardly foreign. Within the United States, states, counties and municipalities have long competed for jobs on the basis of government-regulated factors: tax incentives, environmental waivers, infrastructure subsidies and so on. Still, the

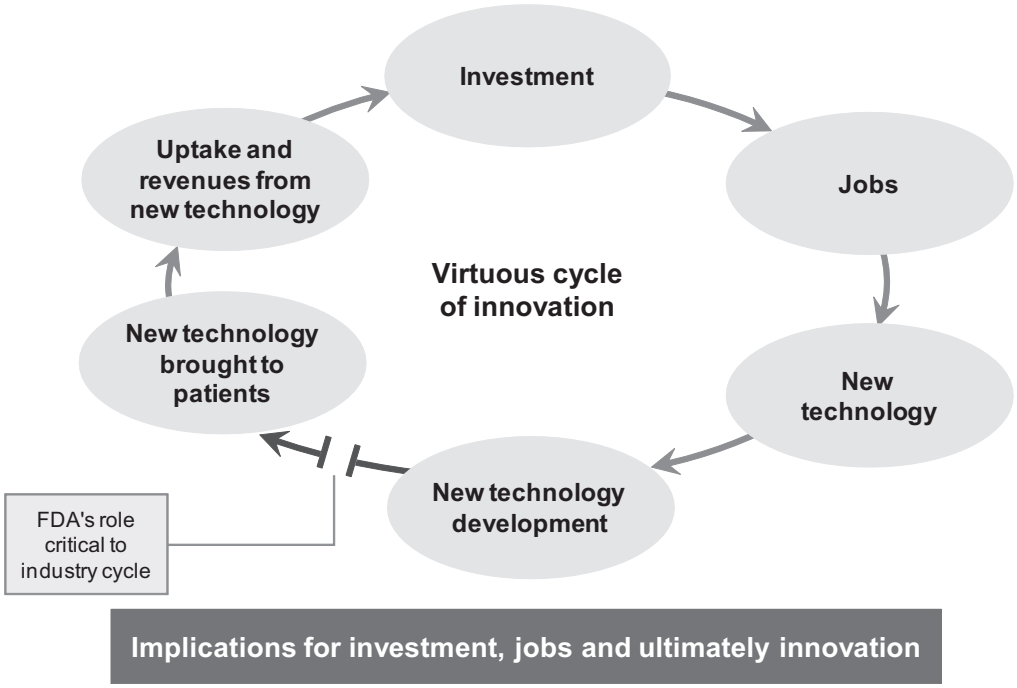


FIGURE 16. Consequences of Slow Regulatory Process on Innovation Cycle.

strategy of adapting regulation of biopharmaceuticals and medical technology with an eye toward business development is relatively new.

Biomedical Innovation

The idea that regulation strongly influences the entire investment-product cycle has not historically been a factor guiding the FDA or, for that matter, Congressional policy. Nevertheless, a well-managed regulatory body can help states or nations gain competitive advantage in technology-based sectors of the economy. It also is a critical factor in ensuring that the cycle of innovation perpetuates (Figure 16).

The 20th century is strewn with examples of American inventions — from the transistor (invented at Bell Labs) to the lithium ion battery — that ultimately became the basis not for America but for industries offshore. The past decade has demonstrated just how fluid the biomedical industry is in the early 21st century. Members of the U.S. biomedical community believe that it is imperative for Congress, the FDA and industry to act quickly to maintain the country's dominance in biomedical advancements and know-how.

CALL TO ACTION

The FDA and its regulatory policies profoundly influence the current state and future strength of the U.S. biomedical industry. It is, indeed, part and partner in the dynamic ecosystem of biomedical research and innovation. Through changes in external factors — including the tightened economic climate, heightened public distrust of regulators and a focus on risk over benefits — the Agency has come under close and often harsh scrutiny. At the same time, it has been burdened with added responsibilities, often without clear standards for success. The FDA's performance has been compromised in its efforts to absorb and accommodate these changes. Its regulatory processes have become unpredictable and slow, which has had enormous and far-reaching effects on the American biomedical industry.

Twenty years ago, Congress recognized a crisis at the Agency and developed legislation to solve it. As the 112th Congress convenes and preparations begin for PDUFA and MDUFMA reauthorization, it is imperative that legislators, the Agency, industry leaders and patient advocates again come together with the will and ideas to restore FDA performance — to restore, support and sustain a strong, science-based Agency and efficient, transparent and predictable review processes to ensure safe and innovative treatments, technologies and therapies for patients in need.

Begin Critical Discussions

The place to begin is a discussion about reinstating regulatory efficiency through establishing more transparency, consistency and predictability throughout the application and review processes. This task must include interactions and procedures at the reviewer, manager and Agency leadership levels. The FDA should be encouraged and empowered to provide more upfront guidance and communication with sponsors regarding approvability. And new policies and procedures should include standards and timelines for approval.

Through the early years of the user fees era, the FDA's development requirements were relatively straightforward and understood. Recently, however, the process has become much less clear. In particular, there has been notable lack of consensus about the appropriate balance between benefits and risk. All medical interventions run some risk of harm, yet a common industry criticism holds that the FDA is overly risk averse. Many industry observers characterize the Agency as having a "zero-risk" mentality — to the point of discouraging beneficial products and biomedical innovation.

Perhaps a better way of framing the issue would be to distinguish between direct versus indirect risks. In this respect, the Agency overwhelmingly focuses on direct risks of drugs and devices: side effects, adverse events and technical product failures. These are comparatively discrete and easy to observe.

Indirect risks — distortions in the regulatory process, for example — in contrast, have a much longer time horizon and may be difficult to measure. How should one calculate the public health loss if investors and companies avoid an important disease because the FDA's demands for clinical data are so extensive and its standards for approving new drugs so uncertain?

Everyone would gain if the FDA and industry developed a shared understanding of "benefit/risk balance." This principle works reasonably well in the broader consumer marketplace in ways that enable manufacturers of automobiles and household appliances to thrive. It is time to define the boundaries of society's expectations of acceptable risks and the Agency's responsibility in approving the most beneficial therapies.

Another key topic of discussion must include the costs of regulation, direct and indirect. The direct costs of regulation fall into three categories: (a) the portion of federal taxes on corporations and individuals that go toward funding FDA appropriations; (b) drug and device user fees; and (c) the costs imposed on drug and device firms that hire regulatory affairs professionals, support staff and consultants who manage and navigate the FDA approval process. As for the latter, inefficiencies at the Agency inevitably create mirror inefficiencies within companies.

Harder to estimate are the indirect costs of regulation, which run from increased costs of capital for FDA-regulated startups to the costs incurred by patients when beneficial products are unnecessarily delayed. As Congress seeks paths to create new jobs and a more business friendly environment, the costs of the regulatory system should be carefully weighed. As the global economy grows ever more connected, American leadership in the biopharmaceutical and medical device industries faces intense competition: for capital, for markets, for talent and for jobs. As these competitive forces gather momentum, investors, managers and policymakers ignore them at their peril. If FDA regulation is just one factor among several, it nonetheless can be pivotal.

Fine-tune Previous Legislation

The user fee systems established by PDUFA and MDUFMA have been largely successful. In preparation for their 2012 renewals, the time is right to evaluate and, where appropriate, correct any measures within those acts that have detracted from the FDA's performance. (As discussed earlier, these measures include provisions of FDAAA such as REMS and stricter advisory committee conflict of interest rules.) The new user fee legislation should, instead of creating expansive new authorities and responsibilities requiring even higher user fee levels, help re-center the FDA to its primary mission and core competencies, addressing the serious inefficiencies and performance breakdowns of recent times.

Industry is committed to continuing and strengthening its partnership with Congress and the Agency. Near-term legislation that encompasses all three entities' concerns and goals will have enormous impacts on the biopharmaceutical and device community. Working together, Congress, the Agency and industry can assure the sector's immediate ability to retain and create jobs, secure financing and generate revenue and its long-term success in continuing U.S. leadership in innovation and international competitiveness while maintaining the high standards of safety and effectiveness that doctors, patients and their families also expect.

APPENDIX A: HISTORY AND MISSION OF THE FDA IN REGARD TO MEDICAL PRODUCTS

The FDA's history dates back to 1906, when Congress passed the original Food and Drugs Act that established the first national regulatory system under the Bureau of Chemistry in the USDA. Under the Constitution's commerce clause, Congress claimed authority to regulate food and drugs involved in interstate commerce and to prohibit distribution of mislabeled and adulterated products. In 1930, the Bureau was expanded and reorganized as the Food and Drug Administration. The pivotal change for the Agency, however, came in 1937-38 as the result of a public health disaster caused by an untested proprietary medicine called Dr. Massengill's Elixir Sulfanilimide that caused 73 deaths. Congressional response to this tragedy was to replace the 1906 Act with the federal Food, Drug, and Cosmetic Act of 1938, which empowered the FDA to evaluate the safety of new drugs *before* they went on the market. Following the thalidomide birth defect tragedy, Congress enacted the Drug Amendments of 1962 to strengthen the 1938 provisions by requiring proof of effectiveness as well as safety and to prohibit marketing any new drug until FDA approved a new drug application for the product.

As for medical devices, the 1938 Act for the first time extended FDA's authority to regulate them, although it did not provide for pre-market review or approval. Congress reconsidered devices in 1962 and came close to legislating requirements for pre-market approval. But the process was sidetracked by the thalidomide birth-defect tragedy that focused attention on drug safety. In 1969, the U.S. Supreme Court issued a landmark decision in the *United States v. Bacto-Unidisk*, ruling that the FDA could regulate an antibiotic sensitivity disc as a drug. To determine the best approach to device regulation, President Richard Nixon convened a group of experts, the Cooper Committee, which reported that devices differed substantially from drugs and therefore needed a separate system of regulation.
The Committee recommended the three-tiered risk classification scheme that Congress incorporated into the Medical Device Amendments of 1976. While this law has been amended several times, the statute's basic structure remains intact. Since 1976, drugs and devices have been considered categorically distinct, with separate regulatory pathways for each.

Creation and authority	• Bureau of Chemistry created from the 1906 Food and Drug Act, enforcing prohibition of interstate transport of adulterated[1] / misbranded food and drugs • Agency reorganized to the current day Food and Drug Administration in 1927 • The agency's powers were reinforced in 1938 with the Food, Drug, and Cosmetic Act, in which the FDA was mandated with pre-market safety review of all new drugs – this law remains central to the agency's current regulatory authority
Mission	• Current responsibilities include regulating and supervising food safety, prescription and over-the-counter pharmaceutical drugs, biologics, vaccines, medical devices, dietary supplements, tobacco products, blood transfusions, electromagnetic radiation-emitting devices, veterinary products, and cosmetics • The FDA is currently led by Dr. Margaret Hamburg, Commissioner of Food and Drugs
Review of drugs and medical devices	• The Center for Drug Evaluation and Research (CDER) is responsible for monitoring three types of drug products: new, generic, and over-the-counter • The Center for Biologics Evaluation and Research (CBER) is responsible for monitoring biologics products including vaccines, blood, tissue, and gene therapy • The Center for Devices and Radiological Health (CDRH) is responsible for the premarket approval of all medical devices, as well as overseeing the manufacturing, performance and safety of these devices

1. Adulterated refers to those in which the "standard of strength, quality, or purity" of the active ingredient was not either stated clearly on the label or listed in the United States Pharmacopoeia or the National Formulary

APPENDIX B: FDA STRUCTURE AND APPROVAL PROCESS

	Drugs		Devices	
	NDA	BLA	510(k)	PMA
Type	Small molecule drugs, including NMEs	Biologic drugs, including NBEs	Class I and Class II devices with predicate design	Class III (riskier) devices
Review authority	CDER	CBER/CDER	CDRH	CDRH
Approval criteria	Scientific review Clinical studies	Scientific review Clinical studies	Manufacturing standards Clinical studies (optional)	Scientific review Clinical studies Manufacturing standards
Application types	Orphan Drug Fast Track Priority Review Standard Review	Orphan Drug Fast Track Priority Review Standard Review	Original Modification Humanitarian Use	Original Modification Humanitarian Use

Note: NDA = New Drug Application; NME = new molecular entity; BLA = Biological License Application; NCE = new chemical entity; CDER = Center for Drug Evaluation and Research; CBER = Center for Biologics Evaluation and Research; CDRH = Center for Devices and Radiological Health

The Present FDA Organizational Structure:

- The Center for Drug Evaluation and Research (CDER) monitors three types of drug products: new, generic and over-the-counter.
- The Center for Biologics Evaluation and Research (CBER) regulates biologic products including vaccines, blood, tissue, cellular and gene therapies.
- The Center for Devices and Radiological Health (CDRH) is responsible for the regulation of all medical devices; it also oversees the manufacture, performance and safety of devices and some diagnostics.

Working through these Centers, drug and device developers take one of four distinct approval pathways to obtain approval for their products to enter the U.S. market.

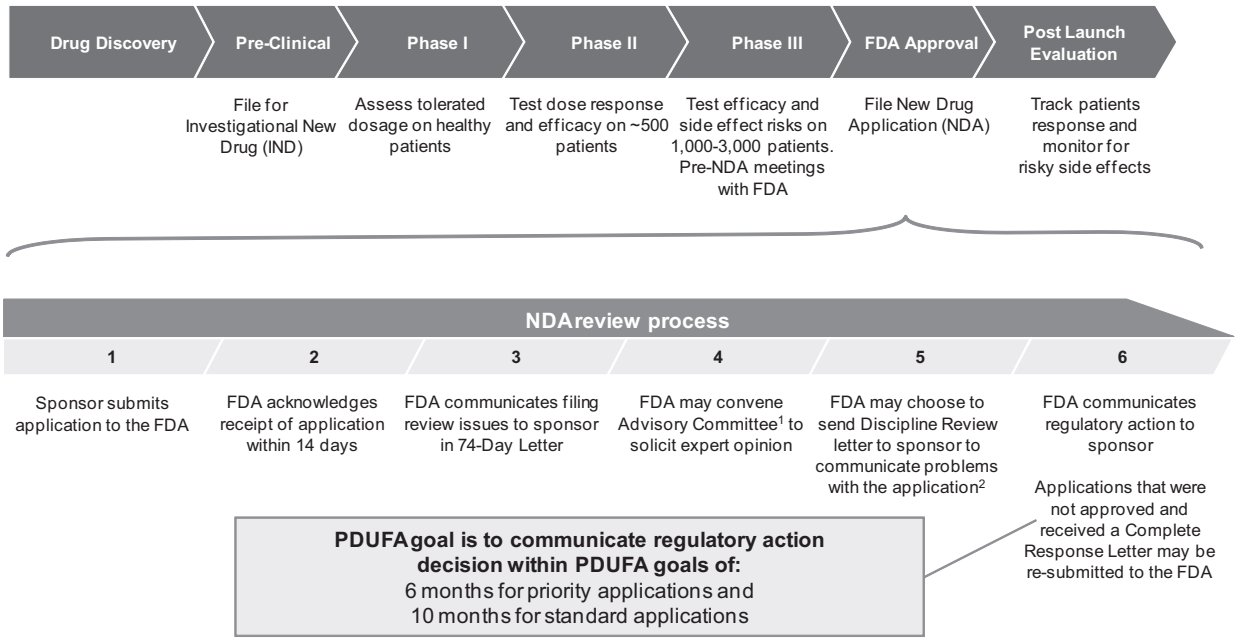
Drug Approvals

There are two approval pathways for drugs to enter the U.S. market:

New Drug Applications (NDAs) for traditional "small-molecule" drugs and Biologic License Applications (BLAs) for biotechnology products and cell therapies. The development process is essentially the same for both.

Device Approvals

For regulatory purposes, the FDA divides medical devices into three classes. Some class I (low risk) and most class II (moderate risk) devices require a "premarket notification" to obtain what is called a 510(k) clearance. Clinical data to show safety and efficacy are increasingly required for 510(k)



1. Particularly for applications where drug is first member in class, if clinical studies involve novel clinical or surrogate endpoints, or if application raises significant safety, efficacy or public health issues. 2. This step does not necessarily temporally follow meeting of the Advisory Committee
Source: "Guidance for Review Staff and Industry: Good review management Principles and Practices for PDUFA products"

APPENDIX B. Overview of FDA's Drug Approval Process.

clearances, and interviews with industry executives suggest that in a number of cases, the Agency is requiring increasingly complex information. Obtaining such information is expensive and time consuming, making the process more costly and lengthy.

Class I and II devices can be evaluated based on design and test data and a comparison to currently available technology. They can be cleared if they are found to be "substantially equivalent to [a device] legally in commercial distribution in the United States."[20]

High-risk, Class III devices are not eligible for this route to market and must undergo a full premarket-approval (PMA) evaluation. Similar to the process for new drug applications, PMAs call for clinical studies and substantial data to demonstrate the products' safety and effectiveness.

More specifically, the FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure its safety and effectiveness. The three classes and the requirements that apply to them are:

Class I medical devices require the least amount of regulatory control. They present minimal potential for harm to users and are typically simpler in design and manufacturing than Class II or Class III devices and have a history of safe use. These devices are subject only to general controls. General controls cover such issues as manufacturer registration with the FDA, good manufacturing techniques, proper

[20] U.S. Food and Drug Administration. Overview of Device Regulation. Accessed 1/13/11 at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm.

branding and labeling, notification of the FDA before marketing the device and general reporting procedures. Most Class I devices are exempt from the FDA 510(k) regulations. These general controls are deemed sufficient to provide reasonable assurance of the safety and effectiveness of the device; or the device is not life-supporting or life-sustaining and does not present a reasonable source of injury through normal usage. Examples of Class I devices include tongue depressors, arm slings and hand-held surgical instruments.

Class II medical devices are those for which general controls alone are insufficient to assure safety and effectiveness and additional existing methods are available to provide such assurances. Special controls may include special labeling requirements, mandatory performance standards and post market surveillance. Devices in Class II are held to a higher level of assurance than Class I devices and are designed to perform as indicated without causing injury or harm to patient or user. Devices in this class are typically non-invasive and include: X-ray machines, powered wheelchairs, infusion pumps, surgical drapes, surgical needles and suture material and acupuncture needles.

A Class III medical device is one for which insufficient information exists to assure safety and effectiveness solely through the general or special controls sufficient for Class I or Class II devices. Such a device needs premarket approval, a scientific review to ensure the device's safety and effectiveness, in addition to the general controls of Class I. Examples of Class III devices which require a premarket approval include replacement heart valves, silicone gel-filled breast implants, implanted cerebral stimulators and implantable pacemaker pulse generators.

Device class	Application	Clinical requirements	Approval type	Mean time to approval	Examples
Class I Low risk	510(k)	Preclinical Proof of good manufacturing standards, correct branding and labeling	Clearance	3-6 months	Bandages, Tongue depressors, Scalpels
Class II Medium risk	510(k)	Preclinical In addition to Class I requirements, special labeling requirements, mandatory performance standards, and post market surveillance	Clearance	3-6 months	Surgical needles, X-ray systems, Pumps
Class III High risk	PMA	Preclinical → Pilot Trial → Pivotal Trial PMA submitted to CDRH for scientific and clinical review. CDRH determines endpoint of clinical testing and makes recommendation to FDA for final approval decision	Approval	12-24 months	Heart valves, Cerebral stimulators, Pacemakers

Source: FDA Devices Program; BCG analysis

APPENDIX B. Overview of FDA's Device Approval Process.

User Fees

As detailed in the main body of this report, the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee and Modernization Act (MDUFMA) were enacted with the support of industry to provide the Agency with better resources while shortening approval time lines.

	PDUFA	MDUFMA
Background	**In the '90s, FDA experienced backlogs in its drug approval process, delaying the launch of many drugs to market** **This led to "drug lag," whereby drugs were being approved abroad before becoming available for US patients**	**Before MDUFMA, FDA's medical device program suffered a long-term, significant loss of resources that undermined the program's capacity and performance**
Purpose	**Increase the efficiency and timeliness of the drug approval process** **Supplement FDA budget with revenue from user fees** **Hold FDA responsible to meeting performance goals in the drug approval timelines**	**Ensure that safe and effective medical treatments will reach patients more rapidly** **Resourcing to ensure that devices marketed in the US continue to meet high standards for safety and effectiveness**
Key features	**PDUFA I: Reducing Application Review Time (FY 1993-1997)** • Allowed FDA to charge user fees in the form of Application, Establishment, and Product fees • FDA used additional user fee revenue to hire more reviewers and support staff **PDUFA II: Facilitating the Drug Dev. Process (FY 1998-2002)** • Reauthorized FDA user fees for another 5 years **PDUFA III: Refining the Process (FY 2003-2007)** • Gave FDA authority to use PDUFA resources on risk management and post market surveillance for up to 3 years after launch **PDUFA IV (FY 2008-2012)** • Increased user fees • Expanded FDA's authority to use funds for post market surveillance and risk evaluation and mitigation	**MDUFMA I (FY 2003-2007)** • User fees for PMAs and 510(k)s pre-market reviews • FDA performance goals become more demanding over time • Establishment inspections may be conducted by accredited persons (third-parties), under carefully prescribed conditions. • New regulatory requirements for reprocessed single-use devices **MDUFMA II (FY 2008-2012)** • Reauthorized user fees with more predictability • Established more rigorous performance goals for FDA • Decreased fees for small businesses

Source: FDA

APPENDIX B. Overview of PDUFA and MDUFMA.

APPENDIX C: NOTES ON METHODOLOGY

Data sources

US drugs

- Drug name, sponsor, submission date, approval date, priority classification populated from FDA Drug database[1]
- Supplemented by EvaluatePharma for 2006-2010 submissions[2]
- Checked press releases for data points without approval dates to verify current status or date of Complete Response Letter

EU drugs

- Submission dates and approval dates populated from EMA website[3]
- Supplemented from company press releases and secondary sources for drugs approved in Europe but not listed in the EMA website

Calculation of approval times

For applications with verifiable approval dates

- Approval time is defined as time of original application submission to FDA until time of FDA approval letter

For applications that had not yet been approved, an estimation of future approval time was calculated, based on average approval times for submission times from 2006-2010 (or current date, whichever was larger)

- No. mos. post-submission → Est. mos. to approval
- 0-10 → 13 mos.
- 10-15 → 18 mos.
- 15-20 → 23 mos.
- +20 → 27 mos.

Calculation of drug lag

Sample excluded vaccines, imaging agents, plasma products and other drugs where meaningful comparisons between EU and US cannot be made

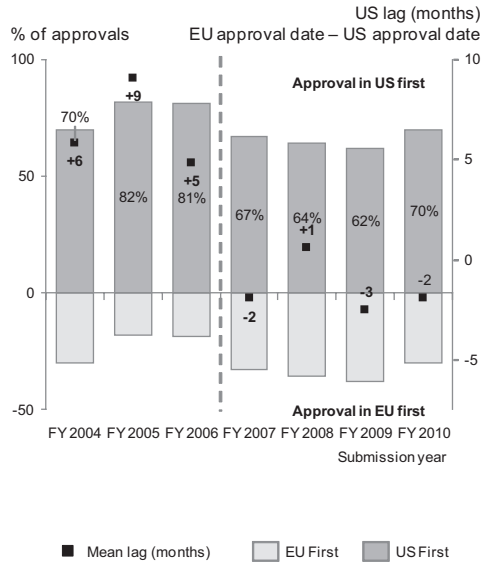
For drugs approved in both authorities difference in approval times calculated directly

For drugs approved in one but not the other approval assumed as of 1/23/11 in the other authority

1. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ 2. EvalatePhrma data query conducted on 10/1/2010 3. http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124&isenabled=true

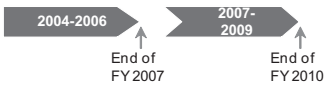
APPENDIX C. Methodology Used to Calculate Approval Timelines.

Data set comprised all drugs approved in either US or EU between 2004 and November 2010



Used statistics to verify whether there was a meaningful difference between '04-'06 and '07-'09

Methodology:



When looking at both time periods from one fiscal year out, are their mean lags and probabilities of approval first in US significantly different?

Statistical tests:

Mean lag (EU approval date – US approval date)	Difference of Means Test
Probability of approval in US first	Chi-squared Goodness of Fit Test

Statistical test results 2004-2006 vs. 2007-2009

	Drugs	510(k)s
Mean lag	Significant difference at the 5% critical level[1]	Not significantly different at the 5% critical level[3]
Probability of approval in US first	Significant difference at the 5% critical level[2]	Significant difference at the 5% critical level[4]

1. Era 1 (u = 6.45, stdev = 17, n = 55) and Era 2 (u = --1.07, stdev = 20, n = 56) 2. Era 1 Pr (US First) = 78% and Era 2 Pr (US First) = 64% 3. Era 1 (u = -8.16, stdev = 20, n = 48) and Era 2 (u = -2.51, stdev = 23, n = 51) 4. Era 1 Pr (US First) = 46% and Era 2 Pr (US First) = 60%
Source: FDA drug database; EMA drug database; Medical device data compiled from 12 different medical device companies, where total sample size n = 205

APPENDIX C. Statistical Tests Used to Validate US/EU Comparisons.

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The **California Healthcare Institute (CHI)**, founded in 1993, is an independent nonprofit organization devoted to researching and advocating policy to forward the interests of California's biomedical community. CHI (www.chi.org) has built a membership of more than 275 leading biomedical companies, academic and research institutions and companies involved in supporting the biomedical community.

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