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BIOCOM

Improving America's Health V

A survey of the working relationship between the life sciences industry and FDA

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Foreword

Bringing a new drug or device to market is no small task. The process can take up to 12 years of research and development (R&D) and cost well in excess of $1 billion. The number of products in development that gain final market approval is minuscule compared with those that begin the development process. The termination rate of experimental drugs in late-stage Phase III clinical trials between 2007 and 2009 doubled the rate from 2004 to 2006, according to CMR International's *2010 Pharmaceutical R&D Factbook*. Of the drugs that reach "first toxicity dose," only one in 10 launches successfully.[1] Against this backdrop, regulators and the industry are seeking ways to make the approval process shorter, less costly and more efficient while maintaining high standards for public health.

Since 1995, PwC has periodically surveyed the life sciences industry on its working relationship with its chief regulatory agency, the US Food and Drug Administration (FDA). This series comprising five surveys is meant to provide insight to FDA and the industry on how to expand trust and build on their relationship.

The most recent survey, concluded in summer 2010, was undertaken jointly by PwC's Pharmaceuticals and Life Sciences R&D Advisory Services team and BIOCOM, the world's largest regional life sciences association, representing 550 Southern California life sciences companies. Building on BIOCOM's strong relationship with life sciences companies and PwC's extensive industry experience and knowledge, this partnership has improved survey participation and enriched the analysis. MassBio (Massachusetts Biotechnology Council) also helped recruit 2010 survey participants. PwC thanks both organizations for their support.

Relationship evolves within the context of healthcare reform, new FDA leadership

The regulatory context surrounding this year's survey was unprecedented. As the survey responses came in, Congress and the Obama administration struggled to reach consensus on healthcare reform legislation that would propel the most significant changes to the industry since the passage of Medicare. The law that emerged March 30, 2010, the Patient Protection and Affordable Care Act as amended (P.L. 111-148), placed numerous new mandates on the industry and more regulatory responsibilities on FDA.

The agency assumed these additional responsibilities as it adapted to new leadership. In spring 2009, President Obama appointed Margaret A. Hamburg, MD, a former New York City health commissioner, to lead FDA as commissioner of food and drugs. In remarks

1 Thomson Reuters Press Release, "Global Pharmaceutical R&D Productivity Declining According to Thompson Reuters, CMR International," June 28, 2010, http://science.thomsonreuters.com/press/2010/cmr_2010factbook/.

to the Food and Drug Law Institute after eight weeks on the job, Hamburg promised to step up enforcement of FDA's regulations. She said she would direct the agency to speed the issuance of warning letters and follow up more promptly. Hamburg also committed to more transparency in enforcement actions.[2]

Survey focuses on long-term dialogue between FDA and industry

Within this context of change, the 2010 survey sought a broad perspective on industry interactions with FDA and looked at their long-term dialogue, recognizing that improving the relationship requires effort from both parties. The most recent surveys explored not only what FDA is doing to provide better guidance and improve processes, but also whether life sciences companies are making proper use of FDA resources and how they are working to improve the FDA-industry relationship. Earlier surveys had a narrower focus in looking at FDA-effectiveness issues, such as delays or impediments to the product approval process and factors that might influence companies to seek approval or manufacture abroad.

This year the survey added new questions about FDA's Sentinel System for monitoring adverse events, incentives for the development of personalized medicine and guidance on data management. These topics have come to the forefront in recent years.

The latest survey also revisited the issue of user fees. Responses to questions relating to the fees should provide useful feedback to Congress as it considers renewal of the Prescription Drug User Fee Act in 2012.

The 2010 survey built on data collected from previous surveys conducted in 1995, 1997, 1999 and 2006. That data formed the backbone of the current survey structure in an attempt to capture the relationship's evolution over the years.

The insight gained from the 2010 survey should help the industry and its regulators identify ways to work together more efficiently. A better working relationship should help bring safer and more efficacious medicines, medical devices and diagnostics into hospitals, clinics, doctors' offices, pharmacies and patients' homes as quickly as possible—all in an effort to improve America's health.

Joseph D. Panetta
President and CEO, BIOCOM

Michael Mentesana
Principal, PwC LLP

2 Margaret A. Hamburg, MD, "Remarks to the Food and Drug Law Institute," August 6, 2009, http://www.fda.gov/NewsEvents/Speeches/ucm175983.htm.

Executive summary

PwC and BIOCOM have surveyed the life sciences industry about its relationship with its chief regulator, the US Food and Drug Administration (FDA), for the fifth time since 1995. Results of the 2010 survey cluster around six key findings:

1. Despite complex scientific, economic and political change, the relationship has improved; but problems remain.

Since the last PwC-BIOCOM survey, many changes have affected the life sciences industry's working relationship with FDA. These include the passage of a healthcare reform law, appointment of a new FDA commissioner and increased public demand for drug and device safety.

Despite these new challenges, the relationship between FDA and the industry has continued to improve. More than three-quarters of survey respondents (78 percent) agree that FDA guidance documents on the product development process have increased their understanding of FDA expectations. The majority of respondents (68 percent) believe that they have done better in incorporating FDA feedback into the development process.

Although the relationship has moved in a positive direction, continuing problems with the approval process have offset some of the gain. Thirty percent of survey respondents saw no improvement in the FDA approval process during the past two years. More than 60 percent said that FDA changed its position on at least one review. Almost as many (58 percent) agreed that politics has too much influence on the approval process. Forty percent of respondents said that FDA denied some approvals primarily because of inadequate resources.

Respondents expressed shortcomings on the part of both the industry and FDA in addressing issues with the detection, assessment, understanding and prevention of adverse events.

2. The industry is unsure of the success of user fees.

The timely topic of user fees, which expire in 2012 unless Congress renews them, also drew some negative industry responses. Of those surveyed, 46 percent do not see that user fees accelerate the review process. A similar percentage think that the purpose and application of user fees lack transparency. Most do not feel that user fees are excessive or cause a conflict of interest.

3. New FDA responsibilities could increase friction between the life sciences industry and its chief regulator.

The new US healthcare reform law assigned additional responsibilities to an already resource-constrained FDA. It required FDA to establish an approval pathway for biosimilars (follow-on biologics). Reform also authorized funding and resources for comparative effectiveness research, which could further complicate the regulatory approval process and strain the relationship.

4. FDA approval process lags scientific and technological advances.

Responses also indicate that the industry feels FDA is not keeping up with rapidly advancing technology. Only 8 percent feel that FDA is doing enough to advance personalized medicine, and the majority agree FDA should increase biomarker development funding. More than half of respondents think that FDA lacks the capability to implement the Critical Path Initiative to bring innovative, high-demand therapies to market quickly.

5. More frequent, open and clear communication could benefit both sides.

Survey results indicate that communication between FDA and the industry falls short on both sides. The industry is not consistent in scheduling presubmission and end-of-phase meetings with FDA, and FDA does not always encourage these meetings. FDA should work to solidify submission requirements and improve communications during the development process. The regulator should make every effort to encourage industry participation in review meetings, especially later in the product approval process when delays and failures are more costly.

Results also pointed to a lack of industry awareness of major FDA initiatives, indicating a general lack of communication on both sides. Some respondents are not familiar with the Clinical Trials Transformation Initiative, the Critical Path opportunity to develop guidance on advanced clinical trial design, or the FDA plan for a Sentinel System to track adverse events.

6. Opportunities abound to improve America's health.

Greater collaboration between the agency and industry could help advance outcomes-driven medicine. More respondents agree than disagree that FDA's all-or-nothing approach to drug approval should be replaced with a limited-launch, living-license process.

With healthcare reform placing greater emphasis on providing value for healthcare dollars spent, the industry must do more to prove the effectiveness of its products and find more innovative methods of care delivery.

The industry will become more involved in managing patient care as it works with payers and providers to ensure personalized diagnosis, treatment and follow-up to improve patient adherence and outcomes.

The FDA and all sectors of the health industries could work together to advance the brave new world of outcomes-driven healthcare and achieve their shared goal of improving America's health.

Key findings

Relationship evolves within context of change on many fronts

Life sciences industry relationship could benefit from closer collaboration in complex times

A time of rapid scientific and technological advancement, unprecedented economic upheaval and political change has increased the need for the life sciences industry and its regulators to work more closely together. Stronger market demand for more innovative and targeted medical treatments has sometimes clashed with the efforts of regulatory agencies to ensure the safety and effectiveness of medicines and medical devices before and after initial approval. While the industry expresses frustration with the approval process, the agency scrambles to hire staff and refine operations to keep up with its growing responsibilities.

Part of the impetus for change comes from high-profile product recalls in recent years, which have raised the level of public distrust in the industry and the agency and caused clamor for greater vigilance for drug safety. FDA has called for black-box warnings on many drugs already approved for the US market. For example, this spring FDA added a boxed warning to the anti-blood-clotting drug Plavix (clopidogrel), alerting patients and healthcare professionals that the drug can be less effective in people who cannot metabolize the drug to convert it to its active form.[3]

The years since the last PwC-BIOCOM survey in 2006 have brought numerous new mandates and responsibilities to FDA and the industry. None is more significant than the recent US leap forward in healthcare reform, which expands FDA's regulatory authority and potentially furthers government influence on drug and device pricing.

This US reform effort reflects the growing power of government and private payers and regulatory bodies worldwide to block the development or use of drugs they do not consider innovative and cost effective. Still reeling from the global economic recession, governments are looking for new ways to drive efficiency and reduce costs across the health industries. Expenditures on drugs through government-sponsored benefit programs, such as Medicare and Medicaid, are coming under increased scrutiny.

The United States plans to finance its healthcare reform efforts, in part, through higher drug rebates as well as taxes and fees on pharmaceutical and life sciences companies. PwC estimates the cost to the industry at $112 billion over the next decade. Rebates for Medicaid recipients and 50 percent branded-drug discounts for Medicare enrollees falling in the Medicare Part D "doughnut hole" threaten to erode revenue gains the industry might see from adding new customers from the ranks of the uninsured. In addition, pharmaceutical companies will pay an estimated $28 billion in new fees based on their share of sales to government programs over the next 10 years. The medical device sector will bear a 2.3 percent excise tax beginning in 2013.

Healthcare reform and additional regulatory and economic developments are pushing the industry along a pathway to a future that looks considerably different from today—one in which the industry no longer develops drugs and devices in isolation but in collaboration with regulators, private and government insurers and healthcare providers to bring only the most needed and cost-effective products to market.

3 FDA news release, "FDA Announces New Boxed Warning on Plavix," March 12, 2010, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm204253.htm.

Figure 1: Impact of healthcare reform on pharmaceutical and life sciences industry

Industry impact, 2010–2019, of US healthcare reform

	$	%
Total branded revenues	$2.6 trillion	
Less: Discounts in coverage gap*	($35 billion)	(1.3%)
Less: Increase in rebates to Medicaid	($35 billion)	(1.3%)
Less: Annual industry fee	($28 billion)	(1.1%)
Less: Follow-on biologics	($25 billion)	(1.0%)
Plus: Increased use from coverage expansions in under-65 population	$11 billion	0.4%
Net impact	($112 billion)	(4.3%)

Source: National Health Expenditure Accounts, PwC calculations

*Includes increased revenues from Part D coverage improvements

Working relationship continues to improve, but problems remain

Despite this increasingly complex regulatory environment, 2010 survey results show that the FDA-industry relationship has continued to improve—although perhaps not as strongly as the previous survey indicated. More than one-third of survey respondents (38 percent) agreed that their working relationship with FDA has improved during the past two years; but 40 percent more were neutral on their response to this question, and 12 percent disagreed. These results could indicate some erosion from the survey in 2006, when the majority of respondents (70 percent) had seen improvement during the previous six years. The shorter time covered by the 2010 survey, however, could account for the less positive response. The 2010 survey asked participants to evaluate the past two years rather than the past six.

Figure 2: Overall FDA-industry working relationship improved

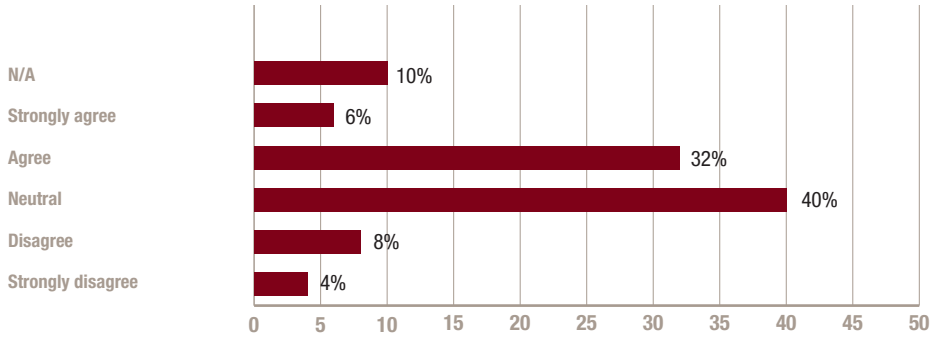


Figure 3: Steps companies have taken to improve their relationship with FDA

Note: Participants were asked to select all answers that apply.

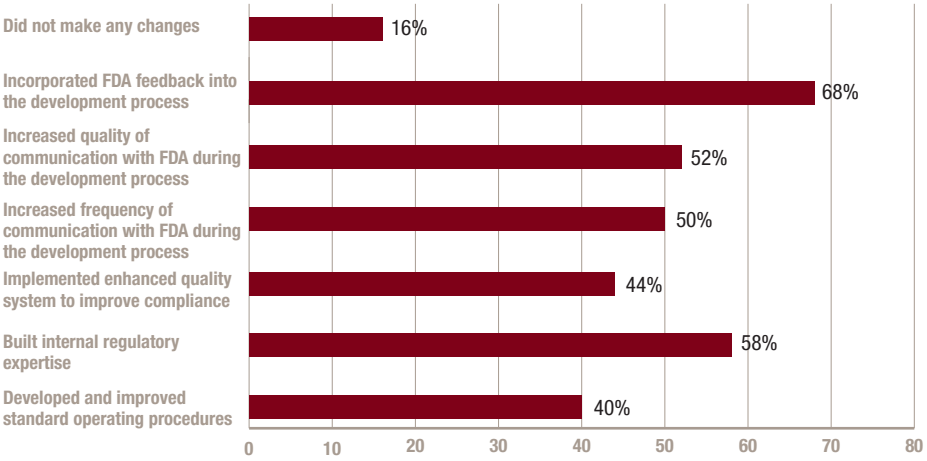


Figure 4: Areas of most improvement by FDA during past two years

Note: Participants were asked to select all answers that apply.

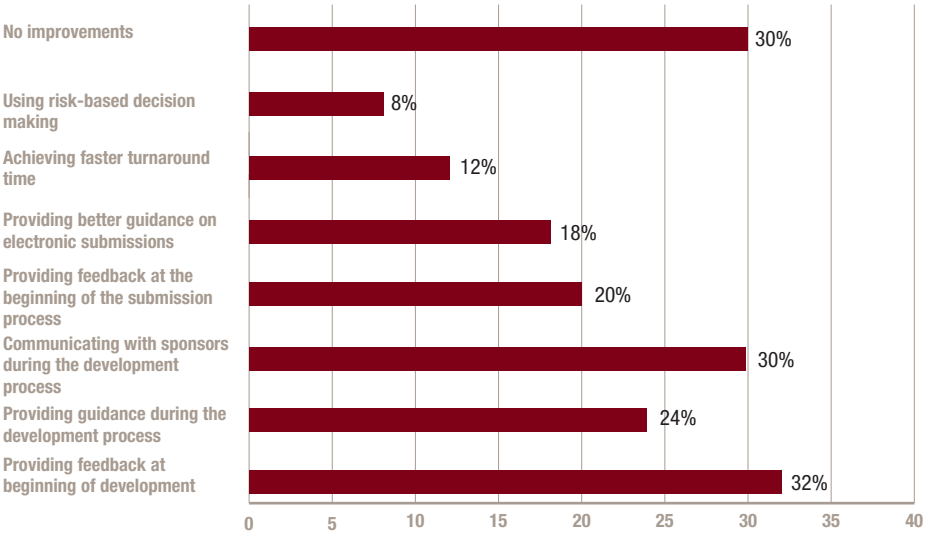
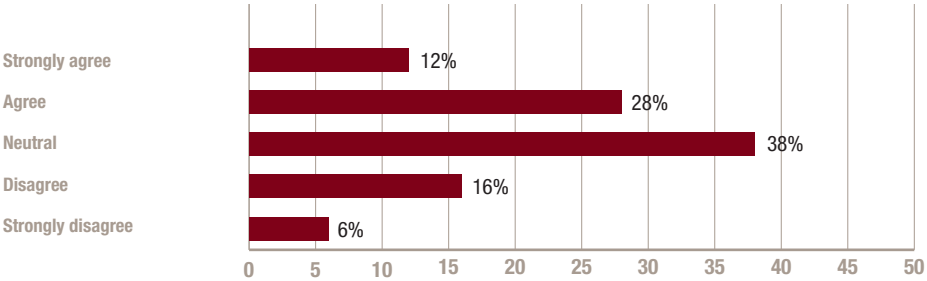


Figure 5: Some product approvals denied because of FDA's inadequate resources



More positively, half of 2010 respondents said they had improved the frequency and quality of their communication with FDA during the development process, and 68 percent had incorporated FDA feedback into that process. Approximately 80 percent agreed that FDA is providing better guidance documents relating to the product development process.

Looking at the agency's role in the development process, only 32 percent of respondents felt that FDA had improved in providing feedback at the beginning of the process, and only 24 percent saw improvement as development progressed. A minority of 12 percent felt FDA was achieving faster turn-around time. Significantly, 30 percent saw no improvements by FDA.

These responses suggest that ongoing struggles with the review process remain. The response to another question related to product approvals indicates that some challenges remain in the relationship. Almost twice as many people agreed (40 percent) than disagreed (22 percent) that FDA denies some product approvals primarily because of inadequate review resources.

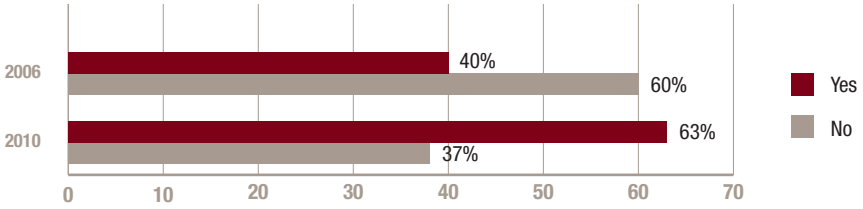
Two post-2006 developments could account for the less positive industry responses to this survey:

1. The 2007 FDA reauthorization (FDAAA) required new safety components for the review process. FDAAA added statutory requirements that increased pre- and post-market review process steps, added new deadlines and effectively increased the review workload. Product approvals fell to 18 that year, the lowest level since 1983.

2. FDA failed to meet Prescription Drug User Fee Act (PDUFA) performance goals in 2008. The agency stated that the delay in approvals was the result of the need to hire, train and integrate new staff and implement the safety legislation (FDAAA) approved by Congress in 2007.[4] The agency approved 24 new molecular entities and biologic license applications in 2008 and 25 in 2009.

Furthermore, more than 60 percent of respondents said that FDA changed its position on at least one review, which was up from 40 percent in 2006. Survey respondents said that FDA often came back to them during the review process to request additional information. Approximately 48 percent experienced a break of continuity in at least one review.

Figure 6: FDA changed its position on at least one review



Public distrust surrounds agency and industry

The media, public and politicians have pointed to an increase in adverse events (harmful drug reactions) as evidence that the industry and its regulators are not doing enough to ensure drug safety and that the agency too often yields to industry influence. From 1995 through 2004, adverse event reports to FDA grew at an average annual rate of 12 percent. Some of this increase, however, could be the result of greater awareness of reporting requirements in the medical community, better reporting practices and the sheer increase in drug consumption.[5]

Only 40 percent of survey respondents agree that the industry is doing enough to address issues with the detection,

Figure 7: The industry is doing enough to address issues with the detection, assessment, understanding and prevention of adverse events

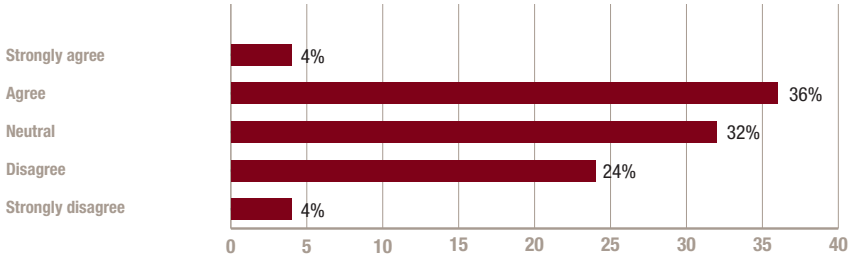
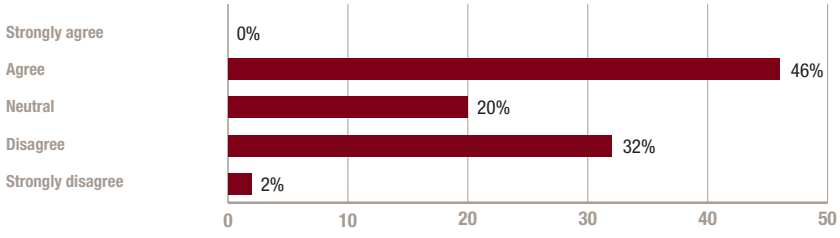


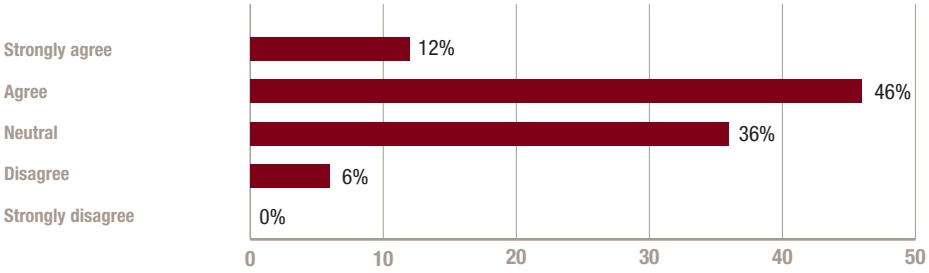
Figure 8: FDA is doing enough to address issues with the detection, assessment, understanding and prevention of adverse events



4 FDA, FY 2008 PDUFA Performance Report, http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm209305.htm.

5 PricewaterhouseCoopers, "Unlocking the power of pharmacovigilance: An adaptive approach to an evolving drug safety environment," 2006.

Figure 9: Politics has had too much influence on drug, device and diagnostic approval



assessment, understanding and prevention of adverse events. A slightly larger percentage (46 percent) agree that FDA is doing enough.

A recent Harris Interactive poll measuring corporate reputation found that the pharmaceutical industry's reputation among the public slipped by 2 percent from 2008 to 2009. In a ranking of 13 industries, pharmaceuticals ranked seventh and was the only one showing a decline in reputation for that period. Yet Johnson & Johnson ranked as the second highest in reputation among 60 companies measured in the poll. Reputational dimensions measured in the survey included social responsibility, emotional appeal, products and services, financial performance, and vision and leadership.[6]

FDA's reputation has not fared well recently in the court of public opinion. A March 2010 Pew Research Center poll found that only 22 percent of Americans surveyed said they could trust the government in Washington "almost always" or "most of the time." FDA's percent-favorable rating dropped 17 percent, declining from 75 percent in the Pew Center's 1997-98 poll to 58 percent in the 2010 survey.[7]

PwC-BIOCOM survey responses indicated that the industry feels that politics influences agency decisions. A majority (58 percent) agreed that politics has too much influence on the approval process.

6 Harris Interactive, "The Annual RQ® 2009 Summary Report," April 2010, http://www.harrisinteractive.com/vault/HI_BCC_Report_RQ_2009.pdf.

7 Pew Research Center for the People and the Press, "Distrust, Discontent, Anger and Partisan Rancor," April 18, 2010, http://pewresearch.org/pubs/1569/trust-in-government-distrust-discontent-anger-partisan-rancor.

Industry unsure of success of user fees

The industry echoes some of the public distrust. As FDA lobbies for renewal of the Prescription Drug User Fee Act (PDUFA) before it expires in September 2012, the latest PwC-BIOCOM survey reveals a need for greater transparency about the purpose and application of user fees. Approximately half of survey participants said they were unclear on the purpose of these fees (Figure 12).

Congress enacted PDUFA in 1992 and renewed it in 1997 (PDUFA II), 2002 (PDUFA III) and 2007 (PDUFA IV). PDUFA authorizes FDA to collect fees from companies that produce certain human drug and biological products. Fees range from $771,000 to $1.5 million per drug application.[8]

The agency says that since the passage of PDUFA, user fees have played an important role in expediting the drug approval process.[9] Yet the industry apparently does not share that opinion. Among respondents to the 2010 survey, only 24 percent agree that FDA is applying user fees as intended, and only 32 percent feel that user fees accelerate the review process.

Figure 10: FDA using user-fee dollars as intended

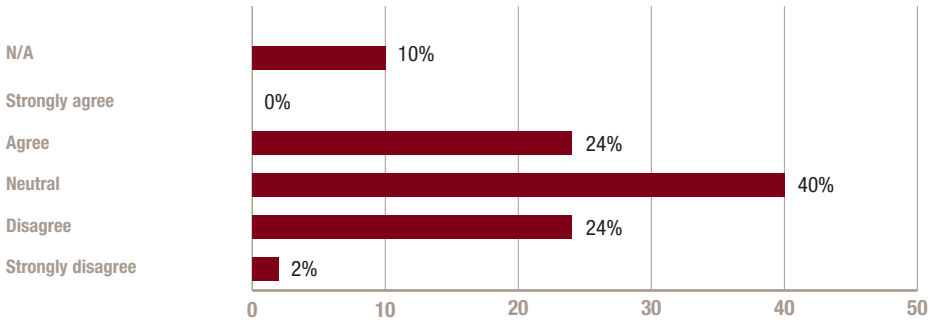
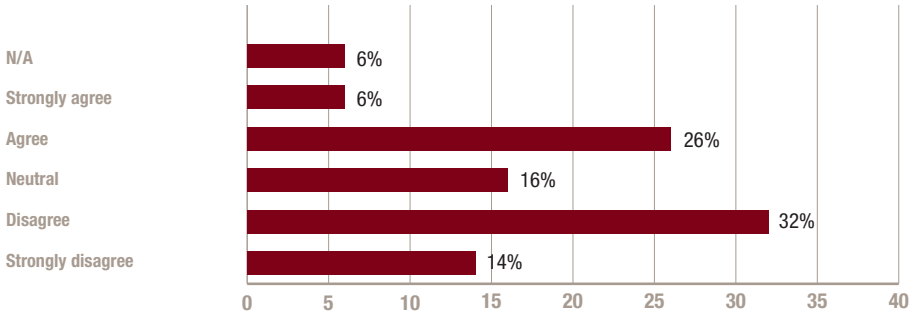


Figure 11: FDA user fees accelerate product review times



8 Department of Health and Human Services, [Docket No. FDA-2010-N-0390], "Prescription Drug User Fee Rates for Fiscal Year 2011," *Federal Register*, Vol. 75, No. 149, August 4, 2010.

9 Department of Health and Human Services, FDA, [Docket No. FDA-2010-N-0128], "Prescription Drug User Fee Act; Public Meeting," *Federal Register*, Vol. 75, No. 50, March 16, 2010.

Figure 12: User fee purpose and use are transparent

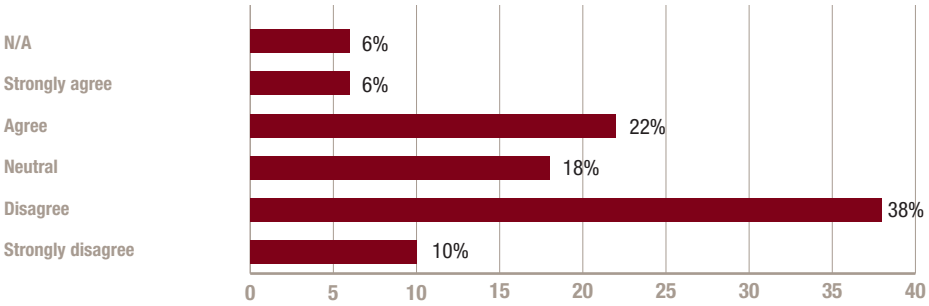


Figure 13: User fees create potential conflicts of interest

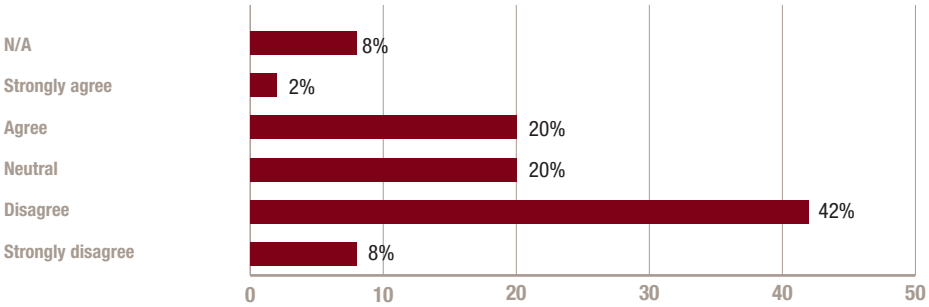
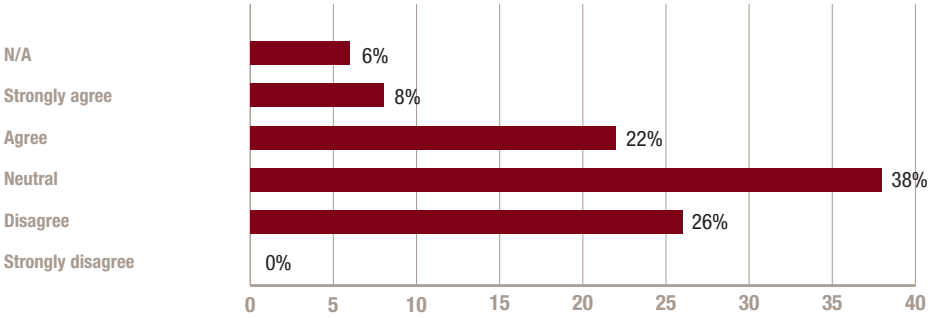


Figure 14: FDA user fees are excessive given the levels of FDA staff time that go into the product review process



FDA says that PDUFA's intent has been to provide additional revenues so that the agency could hire more staff, improve systems and establish a better-managed human drug review process. The goal is to make important therapies available to patients sooner without compromising review quality or approval standards.[10]

Survey results show a clear need for more transparency into the purpose and use of these fees.

Twenty-two percent of respondents feel that user fees create a potential conflict of interest, but 50 percent disagree.

Thirty percent of industry respondents feel that user fees are excessive compared with the time that FDA staff spend on reviews. This response could indicate that the industry might be willing to pay more if companies could see clear evidence that user fees improve the review process.

The most recent iteration of the user fee legislation, PDUFA IV, increased industry fees and expanded FDA's review responsibilities. Among these new duties, the agency was given the authority to require Risk Evaluation Mitigation Strategies (REMS), order safety-labeling changes and require postmarket studies and trials.

10 Department of Health and Human Services, FDA, [Docket No. FDA-2010-N-0128], "Prescription Drug User Fee Act; Public Meeting," *Federal Register*, Vol. 75, No. 50, March 16, 2010.

Figure 15: FDA PDUFA Goals

Original application type		Performance goal	Filed	Performance as of September 30, 2008			Final performance		
				On time	Overdue	Percent on time	On time	Overdue	Percent on time
Priority	All	Act on 90 percent within 6 months	34	13	6	68%	23	11	68%
	NMEs and BLAs		17	7	3	70%	12	5	71%
Standard	All	Act on 90 percent within 10 months	106	20	0	100%	90	16	85%
	NMEs and BLAs		30	10	1	91%	26	4	87%

Source: FDA, FY 2009 PDUFA Performance Report

PDUFA IV also committed FDA to full implementation of good review management principles (GRMPs). These provisions included providing a planned review timeline for premarket review, development of new guidance for the industry on innovative clinical trials, modernization of postmarket safety and elimination of the three-year limitation on fee support for postmarket surveillance.[11]

The agency's record in meeting PDUFA performance goals has slipped with PDUFA IV. PDUFA requires the agency to review and act on 90 percent of submissions within 10 months for a standard application and six months for a priority review. FDA began missing its goals in 2007, a trend that continues today. In its latest report to the president and Congress, the agency said it met or exceeded one-third (4 of 12) of its PDUFA goals in fiscal year 2008 but expected to do better in fiscal 2009. This report showed that FDA did not meet performance goals for priority or standard applications. (See chart from FDA report in Figure 15.) FDA has not issued final fiscal year 2009 results.[12]

As the deadline for renewal of the user fees approaches, the industry should provide constructive feedback to FDA. Although PhRMA, an industry advocacy association, has already endorsed reauthorization of PDUFA, it has criticized FDA for responding slowly to meeting requests and not supplying companies with timely assessment and minutes from meetings.[13]

Public opinion on user fees tends toward ambiguity. Many feel that an industry should not be the primary source of funding for its regulators, yet they do not offer a better alternative. Industry user fees currently account for more than half of the agency's budget. In fiscal year 2008, these fees supported two-thirds of the review cost for human drugs.

11 Ibid.

12 FDA, FY 2009 PDUFA Performance Report, http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm228020.htm.

13 George Koroneos, "Discussions About Drug User-Fees," *Pharmaceutical Executive*, April 14, 2010, http://pharmexec.findpharma.com/pharmexec/News+Analysis/Discussions-About-Drug-User-Fees/ArticleStandard/Article/detail/665248?contextCategoryId=43753&ref=25.

New FDA responsibilities could increase friction between the life sciences industry and its chief regulator

FDA responsibilities expand

At the same time the agency fights to keep user fee revenue flowing, it must allocate already stretched resources to meet its new responsibilities under healthcare reform. The 2010 US healthcare reform legislation cleared the way for an approval pathway for biosimilars, or follow-on biologics. A biologic drug is a protein-based, large-molecule pharmaceutical made from living organisms, and a biosimilar is the generic version. Already resource-constrained, FDA may find it difficult to take on this new responsibility for approving biosimilars.

Comparative effectiveness research gains ground

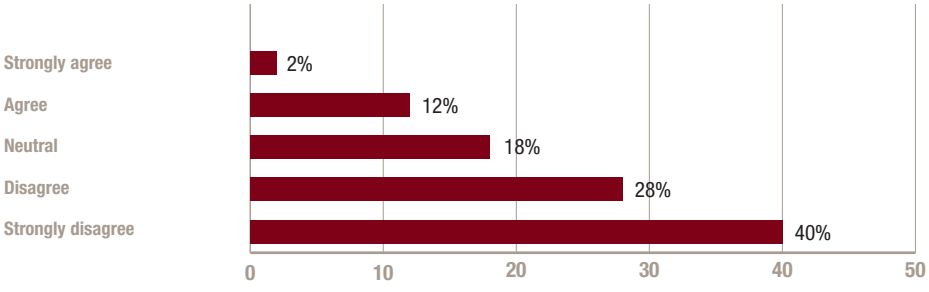
US healthcare reform legislation also has jump-started comparative effectiveness research, which analyzes treatment effectiveness against cost. This type of research potentially puts more power into the hands of healthcare payers and regulators and has significant implications for directing investment in drug and medical device research and development.

The healthcare reform law established a nonprofit, Medicare-funded Patient-Centered Outcomes Research Institute to identify priorities and conduct research that compares the clinical effectiveness of medical treatments. The law did not define FDA's role in this new institute. The US Comptroller General recently appointed 19 members to the institute's board of governors, who will serve alongside the directors of the National Institutes of Health and the Agency for Healthcare Research and Quality or their designees. Appointees representing pharmaceutical, device and diagnostic manufacturers included executives from Pfizer, Johnson & Johnson and Medtronics.[14]

Funded at $10 million in 2010, $50 million in 2011 and $150 million in 2012, the Patient-Centered Outcomes Research Institute could grow substantially by 2013 when its trust fund receives an influx of dollars from new health plan fees. Yet the impact of the institute remains uncertain because the legislation limits its power by stating that its findings may not be used to deny coverage or reimbursement. The new legislation terminates the Federal Coordinating Council for Comparative Effectiveness Research, founded and funded for $1.1 billion under the American Recovery and Reinvestment Act, which had given FDA a seat at the table.[15]

This healthcare reform provision goes against the industry's thinking as reflected in the PwC-BIOCOM survey. A majority of the 2010 survey respondents (68 percent) feel that FDA should not have the authority to approve or deny a drug based on its economic or clinical value (in addition to the agency's traditional responsibility for assessing quality, safety and efficacy).

Figure 16: FDA should have authority to approve or deny a drug based on economic or clinical value



14 "GAO Announces Appointments to New Patient-Centered Outcomes Research Institute (PCORI) Board of Governors," GAO, September 23, 2010.

15 Subtitle D—Patient-Centered Outcomes Research," HR 3590.

Approval process lags scientific and technological advances

Personalized medicine advances

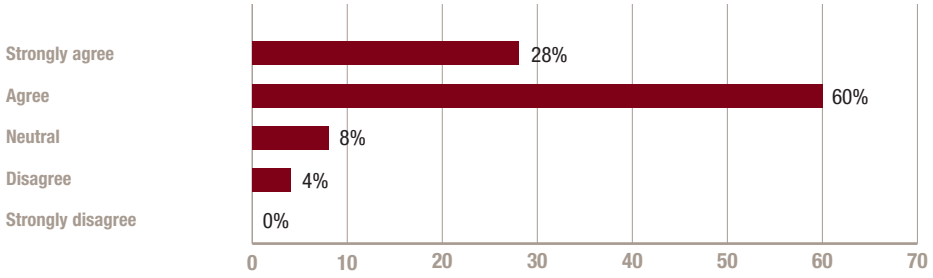
FDA recognizes that it must "participate more actively in the scientific research enterprise directed toward new treatments and interventions" and "modernize" its evaluation and approval processes.[16] Dr. Hamburg has spoken about FDA's commitment to align those processes with scientific and technological advances in personalized medicine.

Speaking to the American Association for the Advancement of Science, Dr. Hamburg said that FDA stands "at the nexus of translating genomics into targeted therapies and new diagnostics, which can lead to better outcomes for patients." She mentioned the shortcomings in the "randomized, controlled clinical trial methods which helped move medicine from the realm of anecdote to evidence over the course of the last half century . . . While we might have a statistically accurate picture, it lacked the nuance we really need to account for human variability. And a statistical average fails to recognize the fundamental truth that patients aren't really homogeneous populations or sub-populations at all, but individuals."

Dr. Hamburg went on to say that "the application of genomics to the field of clinical pharmacology—pharmacogenomics—means that we can put more science and certainty into the regulatory process of reviewing and approving new drugs and biologics. Perhaps then we can see more new drug applications in the pipeline that are more likely to succeed, because the investigators have identified the biomarkers which characterize the patient sub-population most likely to respond to a new therapy."[17]

Most respondents to the 2010 survey (88 percent) agree that personalized medicine will lead to changes in the industry's business model. It will steer the life sciences industry away from blockbuster drugs developed for the masses toward more targeted therapies.

Figure 17: Personalized medicine will change industry's business model



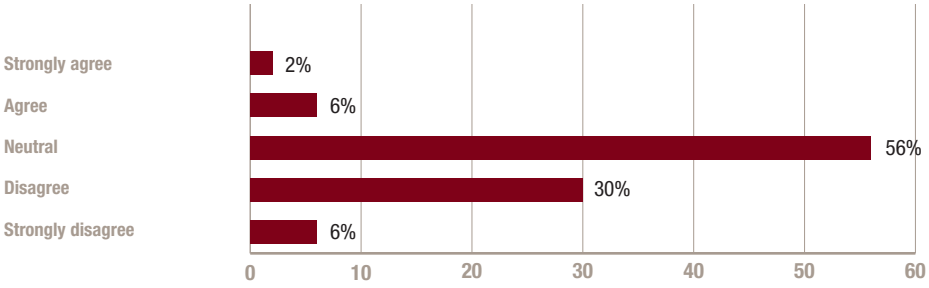
In addition to development of more targeted treatments, PwC predicts that the industry will take a more holistic view of the patient and collaborate with other sectors and nontraditional players in the healthcare space to improve patient outcomes by providing wellness and medication compliance services. The industry will have to deliver diagnostic, counseling and monitoring services to help patients receive and adhere to the care most effective for their specific disease and genetic makeup.

16 FDA, "Advancing Regulatory Science for Public Health," October 2010, www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228131.htm.

17 "Remarks of Margaret A. Hamburg, MD, Commissioner of Food and Drugs at American Association for the Advancement of Science: The Future of Personalize Medicine," Oct. 26, 2009, http://www.fda.gov/NewsEvents/Speeches/ucm191356.htm.

The current regulatory environment is more suited to the old blockbuster model and does little to foster personalized medicine. Only 8 percent of respondents to the 2010 survey feel that FDA is doing enough to advance the personalized medicine development model.

Figure 18: FDA is doing enough to advance personalized medicine



The agency has recently taken some steps, however, to update its regulatory pathways. FDA joined forces with the National Institutes of Health in 2010 to launch an initiative to accelerate the timeline from scientific breakthrough to availability of new, innovative medical therapies. A joint NIH-FDA Leadership Council made $6.75 million available for grants to encourage regulatory science research.[18] The collaboration invited the best minds and research institutions to help develop and apply the new 21st century tools, standards and approaches FDA needs to properly assess the safety, effectiveness and quality of medical products in development.[19]

"Regulatory science is the critical bridge between biomedical research discoveries and new medical products," said Commissioner Hamburg. "But just as biomedical research has evolved in important and powerful ways in the past decades, regulatory science must also evolve. … We must harness advances in science and technology to ensure that we have the most effective and efficient regulatory pathways to address the opportunities before us."[20]

Industry and agency perceive FDA's commitment to personalized medicine differently

As evidence of its commitment to personalized medicine, FDA points to a more established effort to encourage development of treatments for unmet needs, the Critical Path Initiative, which it launched in 2004 to help new drugs reach the market faster. Critical Path calls for rapid incorporation of new science into medical product development and approval pathways. To that end, Critical Path priorities include biomarker development, bioinformatics, quantitative disease models, drug-diagnostic co-development, nanotechnology, clinical trial modernization and indication-specific projects (pain, cancer, rheumatic diseases).[21]

In 2005, FDA and the University of Arizona formed the Critical Path Institute (C-Path), an independent, nonprofit organization, to implement the initiative. Raymond Woolsey, MD, PhD, director of the Arizona Center on Education and Research on Therapeutics, serves as president and CEO of the organization. C-Path is forging collaborations among FDA, academia and industry to develop innovative new testing methods that enable life-saving drugs, devices and

18 NIH, "NIH and FDA Announce Collaborative Initiative to Fast-track Innovations to the Public," February 24, 2010.

19 FDA, "Critical Path 2010 Update," http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm204289.htm.

20 Margaret A. Hamburg, MD, "Remarks at Announcement of FDA/NIH Collaboration," February 24, 2010, http://www.fda.gov/NewsEvents/Speeches/ucm201687.htm.

21 FDA, "Critical Path 2010 Update," http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm204289.htm.

biological products to reach patients faster and with greater safety.[22]

In March 2006, FDA released its Critical Path Opportunities List. Created with public input, the list describes specific areas where the sciences of product development have the greatest need for improvement. The list identifies 76 tangible examples where new scientific discoveries—in fields such as genomics, imaging and informatics (the analysis of biological information using computers and statistical techniques)—can be applied during product development to improve the accuracy of tests that predict the safety and efficacy of potential medical products.[23]

The 2006 FDA report outlined specific areas of Critical Path focus, including:

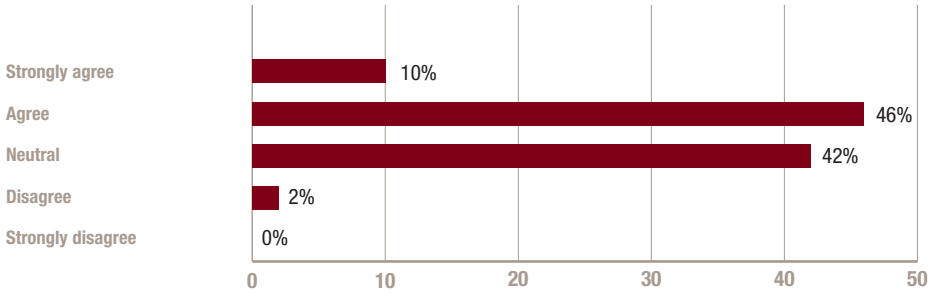
- Develop better evaluation tools such as biomarkers and new assays
- Streamline clinical trials by modernizing the clinical trial sciences to make trials safe and efficient
- Harness bioinformatics (e.g., move from a paper-based to electronic environment for exchanging information and overseeing the safety of FDA-regulated products)
- Move manufacturing into the 21st century using tools such as process analytic technology and nanotechnology
- Develop products to address urgent public health needs, including improved antimicrobial testing, new animal models to test bioterrorism countermeasures and vaccine testing
- Focus on at-risk populations, such as pediatrics[24]

In addition, FDA has collaborated with Duke University to launch the Clinical Trials Transformation Initiative (CTTI) to "modernize the US clinical trials enterprise." Approximately 48 representatives from academia, professional societies, patient and consumer groups, industry and federal agencies are exploring new methods and tools to make the current system more efficient. In November 2009, CTTI and FDA sponsored the first of their annual three-day training courses for clinical trial investigators, drawing 125 participants from around the world.[25]

In 2008, FDA launched its Sentinel Initiative. The agency awarded a contract to Harvard Pilgrim Health (*Mini-Sentinel pilot*) to develop a miniature sentinel system that could pilot a coordinating center and scientific operations and methodologies for tracking adverse events.[26] When fully developed, the Sentinel System will integrate data for monitoring medical product safety.

Despite the Critical Path achievements FDA has reported, more than half of survey respondents feel that the agency lacks the capability necessary to implement the initiative.

Figure 19: FDA lacks capability to implement Critical Path



22 Critical Path Institute, http://www.c-path.org/about.cfm.

23 Ibid.

24 Ibid.

25 Ibid.

26 Ibid.

Industry feels agency could do more to further use of biomarkers

Biomarkers play an important role in Critical Path. The agency maintains a table of valid genomic biomarkers with established roles in drug response. For each biomarker, the table indicates whether pharmacogenomic testing is required, recommended or for information only within the context of a specific drug.

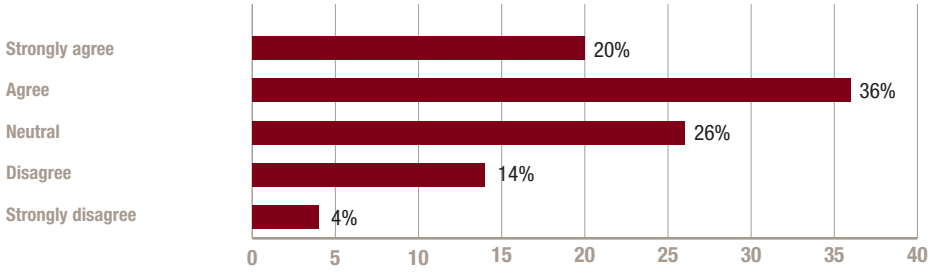
FDA's 2006 "Critical Path Opportunities Report" stated that "targeted investments in biomarker development could help companies identify sooner those product candidates that are likely to fail, while directing more resources to develop promising candidates." The report went on to say, "Biomarkers (incorporated into relevant diagnostics) used to select high-risk populations for clinical trials will also, once the product is on the market, help physicians target treatment to the patients who are likely to benefit most."[27]

The report further noted the importance of biomarkers for patient safety:

Like markers that predict which patients are likely to respond positively to a product, the use of new safety biomarkers can translate rapidly from the experimental setting to the clinic. Patients with a high probability of an adverse effect can be identified and their exposure avoided. In addition, safety biomarkers could be used to monitor patients for emergence of toxicity during treatment, so that therapy can be stopped before harm has occurred.[28]

Despite the agency's efforts to encourage the development of biomarkers, the industry's perception is that the agency is not doing enough. The majority of respondents to the PwC-BIOCOM 2010 survey said FDA should increase funding for the development of biomarkers that measure the progress of disease or the effects of treatment, indicating that the industry feels the agency's current commitment falls short.

Figure 20: FDA should increase biomarker development funding



27 FDA, "Critical Path Opportunities Report," March 2006.

28 Ibid.

More frequent, open and clear communication would benefit both sides

Communications between applicants and FDA during the submission and review process are less than optimal

Responses indicated that the industry was not doing enough to take full advantage of FDA resources. For example, the industry was not consistently asking for presubmission and end-of-phase meetings with FDA. On the other hand, FDA was not consistently encouraging these meetings, which every applicant should have but are not officially required.

The industry could take a more active role in setting up and attending FDA preapproval and end-of-phase meetings. Likewise, FDA should be more consistent in encouraging participation by both parties.

The industry also communicated that it would like to see FDA achieve faster turnaround times for reviews, provide better guidance and improve communications during the development process.

General lack of awareness by the industry of FDA programs indicates communications shortfalls

Responses to several questions in the 2010 PwC-BIOCOM survey indicated a surprising lack of industry awareness of such high-priority FDA initiatives as Critical Path. More than half (58 percent) were not familiar with the Critical Path opportunity to develop guidance on advanced clinical trial design. Fifty-six percent were not familiar with FDA's plan for the Sentinel System. Yet almost the same number felt that the development of such a system would improve medical product safety significantly. As many as 74 percent lacked awareness of the Clinical Trials Transformation Initiative.

Figure 21: Industry always has presubmission and end-of-phase meeting with FDA

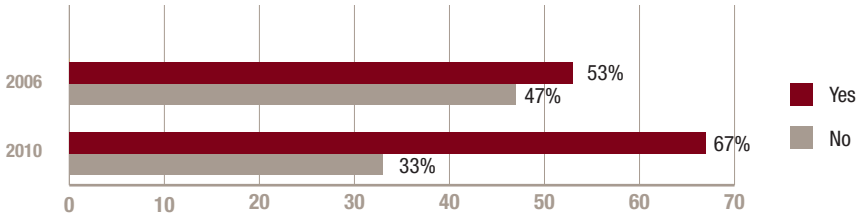


Figure 22: FDA encourages presubmission and end-of-phase meetings

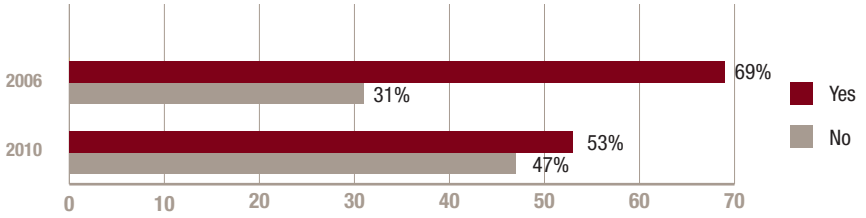
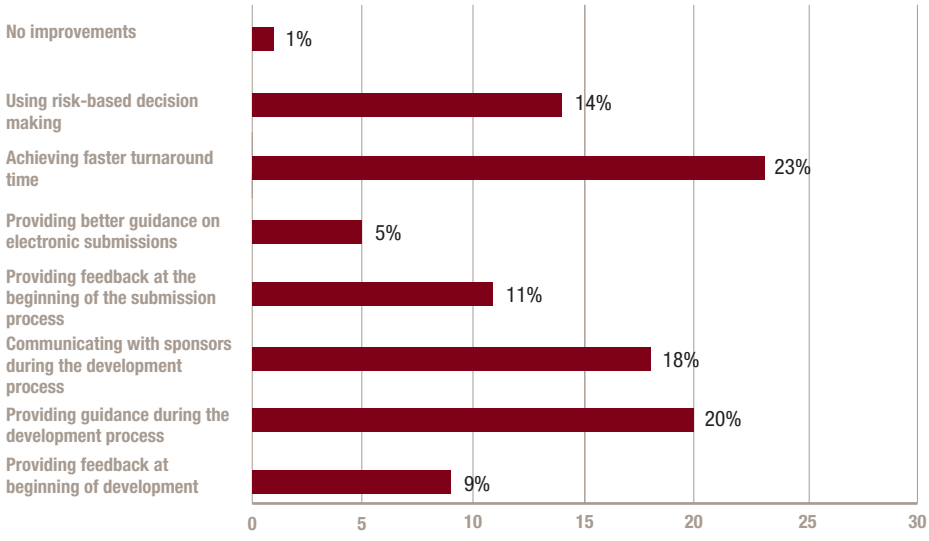


Figure 23: Areas where FDA needs to make the most improvement during next two years

Note: Participants were asked to select all answers that apply.



More direct and clear communication from FDA about major initiatives might alleviate the lack of awareness among some companies of programs that could benefit them. Likewise, the industry could do more to take advantage of the opportunities these programs present for streamlining reporting and approval processes.

Respondents said the industry should help FDA develop guidance documents by participating in agency-sponsored work groups and reviewing and commenting on drafts and proposals.

Opportunities abound to improve America's health

Opportunities driven by collaboration

The life sciences industry is poised to revolutionize healthcare over the next decade through the development of more targeted and effective treatments. If the industry can take full advantage of such programs as Critical Path and improve its working relationship with regulators, it can more readily fulfill the promise of personalized medicine by reducing the time and expense required to bring new treatments to market.

To succeed in the brave new world of outcomes-driven medicine, life sciences companies must pursue development of those drugs and devices for which the demand is compelling. They must be willing to work with regulators to test new products in iterative clinical trials that are smaller and more targeted to specific patient groups. It follows that FDA should adapt its review and approval processes to accommodate creative ways to develop these more complex niche products.

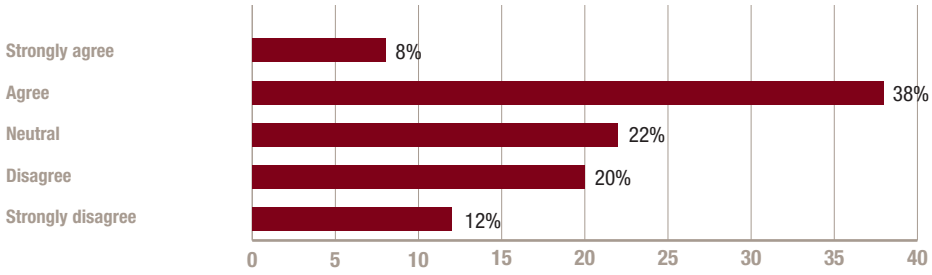
The industry is open to a living-license approach to drug and product approvals. More survey respondents agree than disagree that FDA's all-or-nothing approach to drug approval should be replaced with a limited-launch, living-license process. This process would be based on gradual accumulation of data over time and conditional incremental approvals beginning with evidence from smaller populations. This type of incremental approach could help advance more personalized treatments tailored to individual markets.

Opportunities driven by healthcare reform

The industry will have to prove to regulators and payers that it can deliver value for the dollars invested in healthcare. Cash-strapped governments around the globe are looking for ways to improve the efficiency and effectiveness of their healthcare delivery systems and wring out costs. As evidenced in the 2010 US healthcare reform package, governments are establishing comparative effectiveness and value-based purchasing programs in an attempt to deliver the most cost-effective, clinically proven treatments. The emphasis is moving from sickness to wellness. Policymakers are requiring payers to cover preventive care, such as mammograms and colonoscopies.

Policymakers and payers are taking decision-making power out of the hands of providers by no longer approving or paying for treatments that cannot produce evidence of significantly beneficial results. This trend is requiring drug and device companies to monitor the effectiveness of their products more closely so that they can provide payers with evidence of results. As adoption of electronic medical records becomes more widespread, drug and device companies will be able to provide regulators the outcomes data they demand.

Figure 24: FDA should adopt a living-license approval process



Opportunities driven by industry convergence

To prove the effectiveness of their products, more life sciences companies will enter the realm of health management. They will work with payers and providers to see that patients are diagnosed correctly, that genetic screening is used more frequently to select the most effective treatment and that patients are educated about the proper use of drugs and devices and are given tools, such as smart pill packages and wireless monitoring technology, to help them adhere to prescribed treatments.

PwC's *Pharma 2020* thought leadership series (pwc.com/pharma2020) points to such a future in which convergence blurs the boundaries separating the provider, payer and life sciences sectors and requires a more collaborative approach to the research, development and delivery of medicines. Care will become more localized and customized to the patient as performance metrics, payment, outcomes, incentives, services and treatments address differences in the needs and preferences of individuals. For example, in emerging markets, where demand for better access to care is growing and the diseases of developed nations are becoming more common, providers will use advances such as text messaging, video conferencing and wireless technology to diagnose and treat patients and encourage and monitor their progress.

This more personalized, holistic, patient-centered approach will not only improve America's health, but it will also benefit people worldwide. To realize the potential of this healthcare revolution, the industry and regulators must work together toward their common goal of bringing high-demand, innovative, safe products to market. The health of their relationship has never been so critical.

Methodology

The Improving America's Health V survey continues a series of surveys conducted by PwC in 1995, 1997, 1999 and 2006 in an attempt to show the evolution of the relationship between life sciences companies and FDA. PwC distributed the Improving America's Health V survey electronically to potential respondents across the life sciences industry, including companies that develop biologic, drug and medical device products. Industry trade associations BIOCOM, located in Southern California, and MassBio (Massachusetts Biotechnology Council) helped recruit 2010 survey participants. A total of 50 companies responded.

The survey attempted to gain a broad perspective on industry interactions with the three FDA centers that oversee reviews of life sciences industry product submissions:

- Center for Biologics Evaluation and Research (CBER), which regulates biological products for blood screening and vaccines for disease prevention
- Center for Drug Evaluation and Research (CDER), which regulates prescription and over-the-counter drugs
- Center for Devices and Radiological Health (CDRH), which regulates medical devices, including diagnostics

The survey was divided into two distinct sections:

- Part 1 covered general aspects of the FDA-industry relationship.
- Part 2 covered topics specifically related to investigational or product application submissions. Participation in Part 2 was limited to life sciences companies that had prepared and submitted an application or had one or more applications reviewed by FDA during the past two years.

Survey responses were limited to one per company. Respondents included CEOs, COOs, VPs and directors for regulatory affairs and quality, and other executive staff. PwC collected and analyzed the data, keeping the identity of respondents confidential.

The 50 participating companies represented a cross-section of the industry that ranged from those with fewer than 50 employees to those with more than 5,000. Their annual revenue ranged from less than $10 million to greater than $500 million. The majority of respondents had 200 or fewer employees (76 percent) and annual US sales of less than $10 million (64 percent).

The type of products developed by respondents included the following:

Drugs only	26%
Medical devices and diagnostics	20%
Biologics only	16%
Drugs and biologics	12%
Drugs, biologics and medical devices	10%
Biologics and medical devices	6%
Other	4%
Drugs and medical devices	2%
Clinical research services	2%
Cell-based therapy	2%

About PwC's Pharmaceuticals and Life Sciences Industry Group

PwC's Pharmaceuticals and Life Sciences Industry Group (www.pwc.com/us/pharma and www.pwc.com/us/medtech) is dedicated to delivering effective solutions to the complex strategic, operational and financial challenges facing pharmaceutical, biotechnology and medical device companies. We provide industry-focused assurance, tax and advisory services to build public trust and enhance value for our clients and their stakeholders. More than 163,000 people in 151 countries across our network share their thinking, experience and solutions to develop fresh perspectives and practical advice.

About BIOCOM

BIOCOM is the largest regional life sciences association in the world, representing 550 member companies in San Diego and Southern California, including almost 50 medical device firms. The association focuses on initiatives that positively influence the growth of the life science industry and the development and delivery of products that improve global health and quality of life. This includes initiatives in capital formation, public policy, workforce development, and scientific discovery and development.

PwC contacts

Michael Swanick
US Pharmaceuticals and Life Sciences Leader
+1 (267) 330-6060
michael.f.swanick@us.pwc.com

Michael Mentesana
US Pharmaceuticals and Life Sciences R&D Advisory Services Leader
+1 (646) 471-2268
michael.mentesana@us.pwc.com

Attila Karacsony, Director
+1 (973) 236-5640
attila.karacsony@us.pwc.com

Sean Rooney, Manager
+1 (646) 471-7470
sean.o.rooney@us.pwc.com

BIOCOM contacts

Joseph D. Panetta, President and CEO
BIOCOM +1 (858) 455-0300
jpanetta@biocom.org

Jimmy Jackson, Vice President of Public Policy
BIOCOM +1 (858) 455-0300, Ext. 102
jjackson@biocom.org

Madeleine Baudoin, Associate Director of Public Policy
BIOCOM +1 (858) 455-0300, Ext. 108
mbaudoin@biocom.org

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