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# How the Prescription Drug User Fee Act Supports Life-Sciences Innovation and Speeds Cures

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BY STEPHEN J. EZELL | FEBRUARY 2017

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*PDUFA enables a safe, timely, and efficient process of drug evaluation while applying best practices in regulatory science that play a foundational part in supporting America's role as the world's leader in biomedical innovation.*

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The Prescription Drug User Fee Act (PDUFA) plays a foundational role in America's biopharmaceutical innovation system. By permitting the Food and Drug Administration (FDA) to collect user fees from industry, PDUFA helps ensure the agency is adequately staffed with high-quality personnel and has appropriate workflow and project-management frameworks in place to support making accurate and timely determinations regarding the safety and efficacy of new human drug applications for approval. Moreover, PDUFA plays an important role in fostering innovation, particularly by ensuring that the latest advances in regulatory science are incorporated into the drug-approval process, including by creating pathways for the inclusion of real-world evidence and patient perspectives in the drug-evaluation process. Created by Congress on a bipartisan basis and launched in 1992, PDUFA has since played a transformational role in turning the FDA into the world's leading drug-regulatory agency and in helping to ensure that safe, effective medicines get to U.S. patients faster. As Congress considers reauthorizing PDUFA for the fifth time, lawmakers should recognize the foundational role it plays in underpinning America's biomedical innovation system and improving patient outcomes.

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This report begins by introducing PDUFA and by detailing the critical role PDUFA plays in America's medical-discovery system, documenting the benefits that PDUFA has produced since its inception. It shows how PDUFA has played a key role in accelerating timely patient access to new medicines and in providing a key pillar of a broader supportive environment for life-sciences innovation in the United States. The report then examines several key elements of PDUFA that will come before Congress and the Trump administration in 2017 as part of the law's fifth reauthorization and explains how the continued improvements in "PDUFA VI," as it is known, are positioned to make important contributions to America's life-sciences innovation capacity. Finally, the report addresses some of the specific criticisms that have been leveled against PDUFA and addresses the consequences of a failure to reauthorize the law in a timely manner. Considering the totality of the evidence, the report concludes that PDUFA plays an instrumental and effective role in America's life-sciences innovation system, and that Congress should promptly reauthorize it.

### ABOUT PDUFA

In 1987, the median approval time for a new medicine from the Food and Drug Administration reached well over two and a half years (33 months). Because of parsimonious congressional appropriations, the agency lacked the resources to safely and effectively evaluate new drug applications in a timely manner.<sup>1</sup> To address this, in 1992, Congress passed bipartisan legislation, the Prescription Drug User Fee Act (PDUFA), authorizing the FDA to collect user fees associated with applications from the biopharmaceutical industry for regulatory approval of new human drug submissions.<sup>2</sup> The user fees generated by PDUFA are intended to supplement, not replace, congressional appropriations, although fees generated by PDUFA now account for more than 70 percent of the FDA's funding for reviewing new drug applications. PDUFA also established performance goals for the FDA related to new drug applications (NDAs), biologics license applications (BLAs), drug safety, and the drug-development process itself. PDUFA agreements also contain several procedural and processing goals for improving communication and coordination between the FDA and biopharmaceutical companies.<sup>3</sup>

Over the quarter-century since its founding, PDUFA has provided the FDA with a stable, predictable funding stream that has contributed to significantly accelerated review times, with the median approval time for new medicines falling to approximately 10 months, even while preserving, and, in many ways, making possible the FDA's gold standard for drug safety and effectiveness. Over the past two decades, the program has been instrumental in bringing more than 1,500 innovative medicines to patients.<sup>4</sup> The original 1992 legislation called for congressional review and reauthorization of the PDUFA program every five years. PDUFA has already been reauthorized on a bipartisan basis by Congress on four occasions. In 2017, PDUFA VI will come before Congress for a fifth reauthorization.

The FDA and the biopharmaceutical industry have collaborated to evolve and expand PDUFA's performance goals and objectives over each of its five previous iterations. As the Congressional Research Service (CRS) summarizes the evolution of PDUFA:

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PDUFA II expanded the user fee program's scope to include activities related to the investigational phases of a new drug's development, and to increase FDA communications with industry and consumer groups. PDUFA III again expanded the scope of activities that user fees could support to include both preclinical development and a three-year post-approval period. PDUFA IV concentrated on new measures concerning post-market drug safety. PDUFA V expanded FDA efforts in regulatory science, drug development, drug safety, and information technology.<sup>5</sup>

Likewise, PDUFA VI will contain a number of innovations and improvements, as elaborated upon shortly, including the development and application of 21st-century regulatory-science approaches to drug development, incorporation of greater use of real-world evidence as well as the patient's perspective in medical discovery, and enhancing post-market surveillance to ensure the safety of approved drugs. But before getting into the elements of PDUFA VI, it's important to recount the broader benefits that five PDUFAs have already produced and that can be built upon and extended in PDUFA VI.

### **PDUFA'S BENEFITS**

PDUFA has been a success for patients, public health, and for the American economy. Indeed, according to the Congressional Research Service, "The general view is that PDUFA has succeeded."<sup>6</sup> Likewise, the Program for Enhanced Review Transparency and Communication for New Molecular Entities (NMEs) implemented by PDUFA V has been widely viewed as a success, including by independent reviewers.<sup>7</sup> The following enumerates several of the key benefits PDUFA has produced for America's medical-discovery system.

#### **Accelerating Timely Patient Access to Innovative New Medicines**

The United States operates the most efficient regulatory system in the world—in terms of accuracy and timeliness—when it makes determinations about the safety and efficacy of applications for new drug approvals. As research performed in 2015 by the Regulatory Affairs Professional Society documents, from 2004 to 2013, the FDA consistently led the world's six leading pharmaceutical regulatory agencies in the timeliness of its decisions regarding approvals for new drug applications.<sup>8</sup> As the Food and Drug Administration itself wrote (in correspondence with *The Scientist* magazine in 2014), "The vast majority of the time, the United States is the world's first country to approve novel medicines. In 2013, three-quarters of new drugs approved by the FDA were approved in the United States before any other country."<sup>9</sup> This reiterated findings from a 2012 *New England Journal of Medicine* study, "Regulatory Review of Novel Therapeutics—Comparison of Three Regulatory Agencies," which found that drug applications in the United States get reviewed at least two months faster than they do in Canada or Europe.<sup>10</sup> This means that safe, innovative drugs get to patients faster in the United States than in peer countries.

But it wasn't always this way. In fact, in the late-1980s, 70 percent of new medicines were first marketed overseas and, in the year 1987, the average FDA review time lasted approximately 29 months.<sup>11</sup> At the time, it was not uncommon for pharmaceutical

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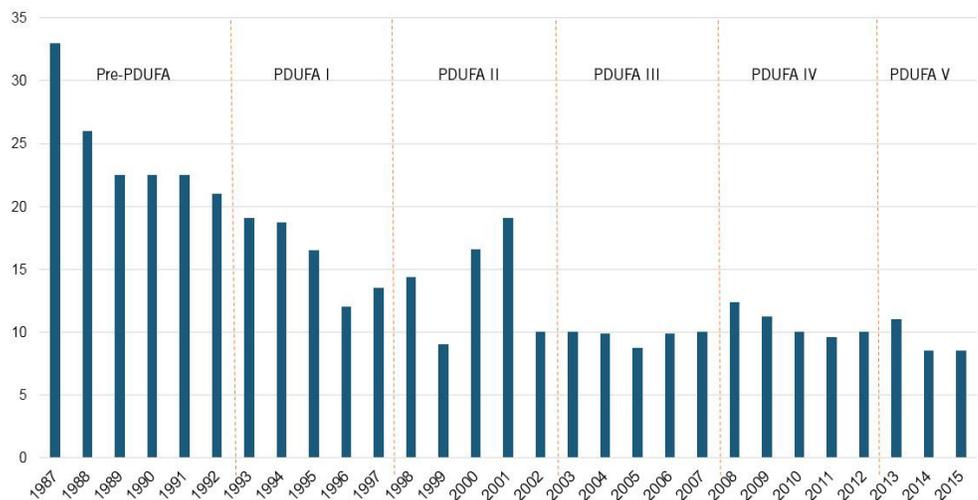
*The timeliness of FDA's decision-making regarding new drug applications means that innovative drugs that do gain approval get to patients faster in the United States than in peer countries.*

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companies to have to wait more than two years for their submissions regarding the clinical trial data and efficacy studies for novel drugs to even be examined. The FDA simply lacked the resources it needed to handle the caseload, particularly when a flood of applications arrived in response to the AIDS crisis of the late 1980s and early 1990s. Accordingly, Congress launched PDUFA in 1992, recognizing that industry user fees could supplement limited general-funds appropriations to ensure the FDA had the needed resources at its disposal to review new drug applications in a timely manner. PDUFA paid dividends almost immediately. For instance, the U.S. Government Accountability Office (GAO) found that the FDA increased its reviewer staff by 77 percent, and drug approval determination times dropped from 27 to 14 months over the first eight years of PDUFA.<sup>12</sup>

By 2015, even while maintaining the FDA’s high standards for patient safety, the median drug approval time at the FDA had fallen by more than a year-and-a-half (from 1992 levels) to under 10 months, as figure 1 shows.<sup>13</sup> PDUFA’s role has been instrumental in ensuring the FDA has the financial and personnel resources to manage its workflow and achieve higher performance targets over the past quarter-century. PDUFA VI seeks to maintain the standard achieved in PDUFA V, with the agency agreeing to “review and act on 90 percent of standard new molecular entity NDA and original BLA submissions within 10 months of the 60-day filing date” and to “review and act on 90 percent of priority submissions within 6 months.”<sup>14</sup>

**Figure 1: Median Approval Times for New Medicines, Months (CDER NME NDAs/BLAs)<sup>15</sup>**



Though not the only factor, PDUFA has certainly been an important part of the reason why innovative new drugs tend to reach patients faster in the United States than in Europe or elsewhere. For instance, Roberts, Allen, and Sigal find in their study, “Despite Criticism of the FDA Review Process, New Cancer Drugs Reach Patients Sooner in the United States Than in Europe,” that “the median time for approval for new cancer medicines in the United States was just six months—and that these new anticancer medicines are typically available in the United States before they are in Europe.”<sup>16</sup> The study undertook a direct drug-to-drug comparison of 35 oncology drugs, 23 of which were approved by both

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*PDUFA isn't about getting drug approvals in a timely manner; it's about making determinations regarding applications for new drugs in a timely manner.*

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the FDA and EMA (European Medicines Agency) from 2003 to 2010 and found that “the FDA consistently took less time than the EMA to review a new oncology medicine.” (The study also found that pharmaceutical companies typically submit their clinical findings to the FDA prior to submitting them to the EMA.) Of the 23 oncology drugs studied and approved by both the FDA and EMA, 20 were approved faster by the FDA, including for groundbreaking anticancer drugs such as Avastin, Nexavar, Sutent, and Sprycel.<sup>17</sup> As the authors note, “The rapid approval of oncology drugs is not accidental, nor is it surprising. The FDA has long sought to conduct more rapid reviews of drugs with greater therapeutic potential, particularly anticancer drugs.”<sup>18</sup> The authors further observed that, “Over the past two decades, the pace at which the FDA reviews drugs has improved considerably, and review times have been shortened. The changes are in large part due to the Prescription Drug User Fee Act of 1992.”<sup>19</sup>

It should be noted that it's not just oncology drugs; other innovative medicines also tend to reach the public quicker in the United States. As Gail Van Norman writes in a 2016 study, “Drugs and Devices: Comparison of European and U.S. Approval Processes,” “analysis indicates that drugs actually reach the public more quickly in the United States than Europe.”<sup>20</sup> That echoes the observation of former FDA Commissioner (2009-2015) Margaret Hamburg that “the FDA's review times of all new drugs are typically shorter than those of the EMA.”<sup>21</sup> Nor is it just with regard to Europe; Australian patients have to wait up to two years longer to access some drugs than patients in the United States, and it wasn't until September 2016 that Australia implemented an expedited drug review process.<sup>22</sup>

As Tulane University's Mary K. Olsen concludes in an in-depth paper, “PDUFA and Initial U.S. Drug Launches,” “the results suggest that PDUFA did improve U.S. patients' access to new medicines by encouraging more first drug launches in the U.S. market.”<sup>23</sup> In particular, Olson notes that quicker FDA reviews effectively lower regulatory barriers to the U.S. market. For instance, faster drug reviews allow firms to enjoy longer periods of market exclusivity, which can increase the expected profitability of new drugs.<sup>24</sup> Olson finds evidence that “these higher expected profits for U.S. drug launches may lead firms to target more drugs for first launch in the United States.”<sup>25</sup> Specifically, her research into initial U.S. drug launches among new drugs approved from 1990 to 2001 found that “declining FDA review times have led to a 14 percent increase in the likelihood of initial U.S. drug launches.” Moreover, she finds, “Other PDUFA-related reforms, such as those reducing drug development times or increasing the probability of approval, have also increased the likelihood of initial U.S. drug launches [by] 31 percent by the end of PDUFA I and [by] 27 percent by the end of PDUFA II.”<sup>26</sup> In short, Olsen finds that the results suggest that PDUFA reforms “were successful in improving drug access for U.S. patients by raising the probability of initial U.S. drug launches.”

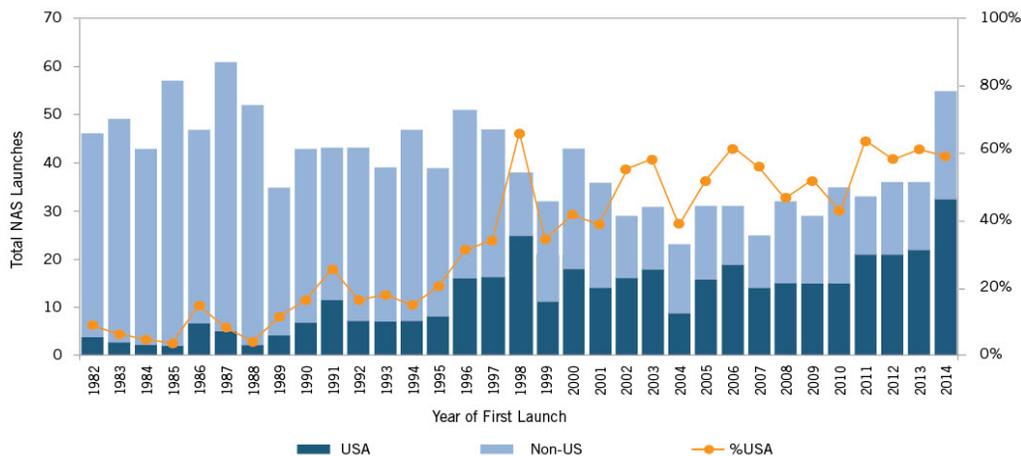
#### **Facilitating U.S. Leadership in Life-Sciences Innovation**

The United States has become the world's leader in life-sciences innovation.<sup>27</sup> For example, between 1997 and 2012, more than half of the intellectual property related to the world's

new medicines was conceived in America, while, in the 2000s, U.S. biopharmaceutical companies introduced more new chemical entities than companies from the next five nations combined.<sup>28</sup> Much of this success stems from the fact that America’s biopharmaceutical sector is extremely research intensive, investing over 21 percent of its sales in research and development (R&D). In fact, strong public- and private-sector investment has made the United States the world’s largest global funder of biomedical R&D investment over the past two decades, a share that some analyses suggested reached as high as 70 to 80 percent.<sup>29</sup>

But it’s not just that America’s government makes significant investments in basic life-sciences research (e.g., over \$30 billion a year through the National Institutes of Health), which private-sector R&D then carries into applied (or “translational”) R&D that turns basic scientific discoveries into new chemical compounds and ultimately new medicines. It’s also that the United States has implemented a robust set of framework policies to support biomedical innovation. This includes, for example, robust intellectual property (IP) protections, such as 12 years of data-exclusivity protection for novel biological drugs, which Congress put in place through the Biologics Price Competition and Innovation Act of 2007. It also includes PDUFA, the transformative 1992 legislation that has helped shape the FDA into perhaps the world’s most efficient and effective drug regulatory agency.

**Figure 2: USA Share of New Active Substances (NAS) Launched on World Market<sup>30</sup>**

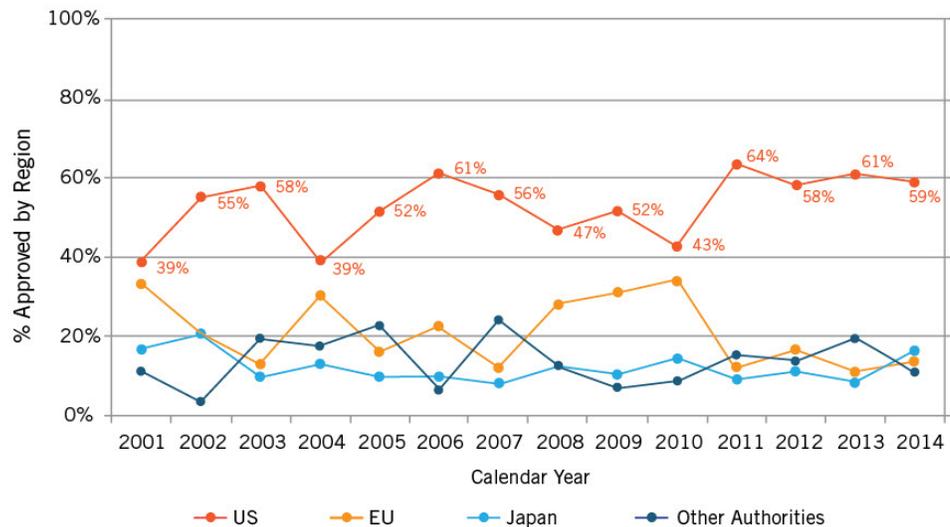


Again, U.S. leadership in life-sciences innovation—just as with FDA leadership in timeliness for drug approvals—was not always the case (nor would it be assured if the effective public policies underpinning it, such as PDUFA or robust public and private life-sciences R&D funding, were to disappear). In fact, as the Legatum Institute’s Shanker Singham notes, “Europe was the unquestioned center of biopharmaceutical research and development for centuries, challenged only by Japan in the post-war period.”<sup>31</sup> In fact, as recently as 1990, the global research-based pharmaceutical industry invested 50 percent more in Europe than in the United States (although by 2006 this would be reversed, with investment in the United States 40 percent higher than in Europe).<sup>32</sup> Moreover, as figure 2

starkly shows, the U.S. share of new active substances launched first on the world market languished at well below 15 percent in the 1980s and into the mid-1990s.

But figure 2 also makes clear the dramatic rise in the U.S. share of new active substances introduced to the world market over the late-1990s and into the 2000s, such that by the 2010s, the United States consistently accounted for an approximately 60 percent share of the total new active substances launched on the world market each year. Figure 3 provides additional detail, plotting new active substances' first launches by region from 2001 to 2014. It shows the United States surpassing the European Union, Japan, and other regions in first launches over this time period.

**Figure 3: Global New Active Substances, First Launches by Region, 2001-2014<sup>33</sup>**



To be sure, many factors inform the dynamics shown in figures 2 and 3, and certainly the most important is the extent of public and private capital invested in biomedical R&D by the U.S. government as well as private-sector entities over the past quarter-century, as the Information Technology and Innovation Foundation (ITIF) writes in its report “Why Life-Sciences Innovation Is Politically ‘Purple’—and How Partisans Get It Wrong.”<sup>34</sup> But an equally important explanatory factor is the ecosystem that the United States has created to support life-sciences innovation, which includes everything from strong intellectual-property provisions, to robust R&D tax credits, to the role PDUFA plays in ensuring the FDA has sufficient resources and access to high-quality personnel to undertake the difficult process of reviewing applications for new drugs in a safe, timely, and efficient manner.

#### Supporting a Key Innovative Sector of the U.S. Economy

America’s biopharmaceutical sector represents one of America’s most innovative and important high-value-added, traded sectors. America’s biopharmaceutical sector supports 854,000 direct jobs and over 4.4 million total jobs (when indirectly supported or induced jobs are counted).<sup>35</sup> The sector shipped exports of \$47 billion in 2015, an amount that has tripled since the year 2003.<sup>36</sup> As measured by Battelle, the overall economic impact of the biopharmaceutical sector on the U.S. economy totals \$789 billion on an annual basis when

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direct, indirect, and induced effects are considered.<sup>37</sup> And, today, U.S. biopharmaceutical companies have more than 3,400 drugs—many first-of-their-kind—under clinical development.<sup>38</sup>

As noted, drug discovery and development is a research-intensive and highly risky endeavor. The biopharmaceutical sector is one of the most R&D intensive of any in the U.S. economy. In 2016, domestic R&D as a percentage of domestic sales reached 24.8 percent (while the sector’s R&D investment as a share of global sales tallied 19.8 percent).<sup>39</sup> In 2014, the sector accounted for 23 percent of domestic R&D funded by U.S. businesses—more than any other sector.<sup>40</sup> In 2015, the industry invested \$58.8 billion in R&D, a significant increase from the \$8.4 billion invested in 1990. This increase is the result of a number of factors, including the difficulty and expense involved in pushing the boundaries of medical science; the opportunities for innovation that have been unlocked by a deeper understanding of the human genome as well as the emergence of biologics-based medicines (drugs derived from and synthesized in living tissue), which have opened new opportunities and pathways to treat certain disease classes (such as breast cancer); and a combination of inflation-adjustment effects and increased costs (e.g., for medical researchers).

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An efficient, transparent, and evidence-based regulatory environment helps attract private-sector investment. Accordingly, a consistent, efficient, and dependable FDA regulatory environment helps ensure that life-sciences R&D—and ultimately groundbreaking innovation—is more likely to be conducted in the United States and that patients will benefit from access to new medicines sooner. If foreign regulatory practices were perceived to be preferable to domestic regulatory policies (as they no doubt were, for example, in the 1970s and 1980s), private-sector investment in life-sciences R&D and innovation would likely follow, meaning jobs and new medicines would be created elsewhere first. In short, PDUFA’s role in streamlining and making FDA review processes as efficient and effective as possible represents an important component of a broader supportive ecosystem that has made the United States the world’s most attractive location for life-sciences R&D and innovation.

## **PDUFA VI**

PDUFA VI seeks to build on the success and experience of the five prior PDUFAs in making FDA review of new medicines even more predictable, efficient, and consistent while maintaining and strengthening the agency’s high-quality safety and efficacy standards. Reflecting a process of two-way dialogue between the agency and the industry, PDUFA VI seeks to incorporate a number of new elements into the drug regulatory review process. Of these, five of the most important elements of PDUFA VI include:

- **Supporting the development and application of 21st-century regulatory science approaches to drug development.** This includes creating a pathway for greater use of real-world evidence (i.e., evidence outside of randomized clinical trials) in regulatory decision-making, supporting innovative clinical-trial approaches, and enhancing biomarker-qualification pathways.

- **More attention to patient-focused drug development.** This includes greater effort to incorporate patient perspectives in the drug development and review process, including making greater use of patient-reported outcomes.
- **Greater focus on supporting rare diseases and breakthrough therapies.** This includes continued application-fee waivers and advanced reviews for medicines that can treat rare diseases, as well as prioritizing the development of breakthrough medicines for patients with life-threatening diseases.
- **Enhancing post-market safety monitoring of approved drugs.** This includes additional resources for the FDA’s Sentinel system, for surveillance of drugs that have already entered the patient population.
- **Workflow and workforce planning at the FDA.** PDUFA helps ensure that the FDA has the resources and skilled talent it needs to develop realistic workforce planning and workflow projections. Ultimately, the goal is to ensure that the FDA has the medical, scientific, and administrative capacity it needs to keep pace with medical innovation and to be able to do so in a predictable way.<sup>41</sup>

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The following provides analysis on these core performance objectives of PDUFA VI, explaining why they are needed and should be looked upon favorably by Congress as it considers PDUFA VI reauthorization.

#### Supporting Development of 21st-Century Regulatory-Science Approaches to Drug Development

The nature of drug discovery has evolved tremendously as the power of information and communications technology (ICT) and high-performance computing (HPC) have transformed both the ability to unlock the morphology of cells and how drugs interact with them as well as the ability to use large data sets (i.e., big data) to gain new insights from longitudinal information on patient populations.<sup>42</sup> This has enabled the creation of so-called “rapid-learning health networks” that have transformed how health-care research gets performed. As Lynn Etheredge of the Rapid Learning Project at George Washington University explains:

Traditionally, health research has relied on in vitro and in vivo methods—lab work and animal and human experiments. The rapid-learning networks add in silico research—using computerized databases and networks with individual-level, clinically rich, and longitudinal data from millions of patients captured in electronic health records. [This is why] NIH Director Francis Collins has recently proposed a new national patient-centered research network with 20-30 million patients.<sup>43</sup>

Etheredge asserts that this heralds a movement toward precision medicine that is primed to revolutionize biomedical research, clinical practice, and public health. Etheredge contends that some of the earliest and most dramatic results have been achieved in pediatric cancers, noting that major childhood cancers used to have mortality rates in excess of 90 percent, but that today life expectancy is approaching [that of] children who have never had a

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cancer. In fact, over the past 30 years, childhood deaths from cancer have declined by 50 percent overall.<sup>44</sup> Etheredge argues that this is in part “a result of an organized research system that reports and learns from the treatment of every child with cancer, and shares those data and experiences for rapid-cycle learning.”<sup>45</sup> Other rapid-learning networks have also made significant advances in disease-specific (e.g., cancer, cardiovascular, diabetes, etc.) as well as genetics-related research. Indeed, “data-driven innovation is rapidly transforming the medical field by helping researchers make important advances in science, enabling physicians to develop and use innovative diagnostics and treatments, and allowing policymakers to improve health care quality and costs for millions of individuals.”<sup>46</sup> Similarly, drug development is speeding up thanks to cloud computing and data analytics, including by helping to identify patients, accelerating data processing and analysis, and cutting clinical trial costs. As a representative of GlaxoSmithKline explained to *BBC*, “Advances in computing and data analytics are providing new opportunities to improve the efficiency of our research and increase our understanding of a disease or a patient’s response to medication.”<sup>47</sup>

But this discussion is really about the increasing opportunity to incorporate so-called “real-world evidence” into the drug-discovery process. Real-world evidence—evidence attained outside of randomized clinical trials (RCTs)—will not only tap increasing volumes of data, but will also weave together different sources of data, such as clinical data, genomic data and socioeconomic data, to yield a better picture of individual patient characteristics and improve medicine’s ability to treat individual patient needs.<sup>48</sup> Real-world evidence is already generating new information that decisionmakers can consider alongside traditional RCT evidence. As part of PDUFA VI, the FDA will consider the possibilities of using “real-world” data as an important tool in evaluating not only the safety of medications but also their effectiveness.<sup>49</sup> The FDA will undertake workshops with key stakeholders, including patients, biopharmaceutical companies, and academia, to gather input into issues related to real-world evidence use in regulatory decision-making. By the end of FY 2021, the FDA intends to publish draft guidance on how real-world evidence can contribute to the assessment of safety and effectiveness in regulatory submissions, for example in the approval of new supplemental indications and for the fulfillment of post-marketing commitments and requirements.<sup>50</sup>

PDUFA VI will also explore the greater use of novel biomarkers as surrogate endpoints, that is, where a biomarker substitutes for a clinical endpoint. (The term “biomarker”—i.e., biological markers—refers to objective and quantifiable characteristics of biological processes that can define a normal or a pathogenic state. A good example of a biomarker is the HER2 positive gene mutation—a biomarker that signals the possible presence of breast cancer in women.)<sup>51</sup> Before the FDA approves a new medicine, researchers must demonstrate the medicine’s safety and efficacy. Specific measures, called clinical endpoints, must be met in order to demonstrate safety and efficacy. A surrogate endpoint is a marker—such as a biomarker or other measure—that is expected to predict, but is not itself a measure of clinical benefit, and can thus be substituted for a clinical endpoint. The use of surrogate endpoints matters because it can accelerate drug development and considerably

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shorten the time required for FDA approval, allowing patients quicker access to promising new medicines. Medicines approved based on surrogate endpoints are typically granted an accelerated approval that is contingent upon the sponsor continuing research, called Phase 4 studies, in order to confirm long-term safety and efficacy.<sup>52</sup>

The identification of biomarkers is vital in the development of medical cures. For instance, biopharmaceutical researchers have focused on identifying biomarkers—such as the HER2 positive gene mutation—for women with breast cancer. By contrast, the treatment of Alzheimer’s disease has been significantly hampered by the lack of easily accessible biomarkers that can detect disease presence and predict disease risk reliably.<sup>53</sup> The lack of a reliable biomarker has been one of the most difficult challenges in Alzheimer’s research, and in part explains why, since 1998, 123 medicines in development for the treatment of Alzheimer’s disease have not made it through clinical trials, and only four have made it through to an approval.<sup>54</sup> Yet the payoff from an Alzheimer’s treatment could be substantial: A new medicine that could delay the onset of Alzheimer’s by five years would reduce the number of people with the disease by approximately 40 percent and save America’s health-care system \$367 billion a year by 2050.<sup>55</sup> That’s significant, given that the financial impact of Alzheimer’s disease is expected to soar to \$1 trillion per year by 2050, with much of the cost borne by the federal government, according to the Alzheimer’s Association report, “Changing the Trajectory of Alzheimer’s Disease.”<sup>56</sup>

Accordingly, PDUFA VI contains provisions designed to enhance the FDA’s biomarker-qualification process, including developing staff capacity to enhance biomarker-qualification review, convening a public workshop on biomarker taxonomy, and publishing an updated list of biomarker-qualification submissions.

#### **Greater Attention to Patient-Focused Drug Development**

Engaging with patient groups to understand the patient’s perspective and experience—the so called “patient’s voice”—from the beginning and throughout research can greatly benefit overall drug development. Specific feedback from patient groups adds value throughout the medical-discovery process, from designing studies, to identifying study participants, even to providing input to regulatory agencies on which outcome measures mean the most to patients.<sup>57</sup> Engaging the patient voice can also help prevent researchers from having to change experiments once they have begun, which often means clinical research is completed faster, saving drug companies time and money and helping innovative cures reach patients faster, according to Bray Patrick-Lane, who leads a public-private partnership called the Clinical Trials Transformation Initiative (CTTI).<sup>58</sup> She notes that the Tufts Center for the Study of Drug Development has documented that a significant amount of money gets wasted by changing clinical trials late in the game or by training doctors and staff at trial sites that never end up enrolling a single patient, and these costs could be reduced if the patient voice were incorporated earlier in the medical discovery process.

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PDUFA VI makes great strides toward integrating the patient voice in the drug development and regulatory decision-making process, doing so in a number of important ways. First, the FDA is investing in staffing dedicated experts within its review divisions who will work with patients and patient advocates to advance their input into policy. Second, the FDA will use a public process to develop guidance on gathering stakeholder feedback about how to best collect patient and caregiver input. Lastly, PDUFA VI ensures that the FDA will conduct additional public meetings on including the patient voice in the development of clinical trials. These important transparency-promoting provisions will ensure the patient remains the center of FDA policy considerations. Greater incorporation of both the patient voice as well as real-world evidence are regarded as perhaps the most transformational elements of PDUFA VI from a scientific perspective.

#### Placing Greater Focus on Rare Diseases and Breakthrough Therapies

Approximately 7,000 rare diseases are known to exist today, yet only 5 percent of these have an approved treatment.<sup>59</sup> Meanwhile, 30 million Americans, around 1 in 10, live with a rare disease.<sup>60</sup> Eighty percent of rare diseases are genetic in origin, and more than half of those affected by rare diseases worldwide are children.<sup>61</sup> The challenges posed by rare diseases are significant, but the good news is that more than 560 medicines are in development for rare diseases today; and that, in 2015, 47 percent of novel new drug approvals were for rare diseases. Moreover, over one-third (37 percent) of the novel drugs approved (in CY 2015 through December) were the first in their class and two-thirds (66 percent) of the novel drugs approved (in CY 2015 through December) were first approved in the United States.<sup>62</sup>

Smart public policies have played an important role in promoting research into and development of treatments for rare diseases. For instance, more than 500 orphan drugs have been approved since the passage of the Orphan Drug Act, which provided a more generous tax credit for R&D into rare diseases. PDUFA has likewise played a role, initially by waiving application fees for medicines to treat rare diseases and by adding in PDUFA V regulatory-science enhancements for rare diseases as part of the New Molecular Entity review model.

PDUFA VI is poised to continue to make significant enhancements to the drug development and approval process for rare diseases. For instance, PDUFA VI will continue to integrate rare-disease program staff into review teams for rare-disease development programs and application reviews. This will include supporting expert insights on new approaches to study and review innovative medicines for rare diseases, including the use of biomarkers as novel endpoints, nontraditional clinical development programs, adaptive study designs, and new statistical approaches. PDUFA VI will also facilitate greater outreach to patient groups and other stakeholders on issues related to rare-disease drug development and review and will task the FDA with providing more information on rare-disease drug approvals and metrics in the agency's annual reports on new drug approvals and PDUFA performance. PDUFA VI will also expand staff training related to

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*PDUFA VI is poised to improve the drug development and approval process for rare diseases.*

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development, review, and approval of drugs for rare diseases as part of the reviewer training core curriculum.<sup>63</sup>

PDUFA has played an important role in supporting medical discovery into breakthrough therapies. As part of PDUFA V, in 2012, the FDA created a fourth expedited program for accelerated drug approvals: the “breakthrough-therapy” designation. (This built upon the “accelerated approval” and “priority review” designations launched in 1992 and the “fast track” designation launched in 1997.)<sup>64</sup> The breakthrough-therapy designation helps expedite the development and review of drug and biological products for serious or life-threatening diseases or conditions when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies. For drugs receiving the breakthrough-therapy designation, the FDA provides “intensive guidance on efficient drug development” and involves senior management to “expedite the development and review” of the therapy. As *The Scientist* notes, the designation can lead to the use of alternative clinical-trial designs, such as adaptive-study designs, or more efficient trials with small patient numbers.<sup>65</sup> In the first three years of the breakthrough-therapy designation, the FDA received 337 breakthrough-therapy requests and granted 104 of them.<sup>66</sup> With regard to the four types of expedited approvals, the vast majority have gone to cancer therapies, which have accounted for 76 percent of priority reviews, 48 percent of fast-track designations, and 30 percent of accelerated approvals since the programs began.<sup>67</sup> PDUFA VI will build on the success of PDUFA V’s creation of the breakthrough-therapy designation and continue to prioritize development of such drugs.

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*PDUFA VI will assist the FDA with hiring and workforce management provisions, ensuring that the agency can recruit, train, and maintain the highest-quality medical and technical professionals with the advanced skills needed to undertake complicated human drug reviews.*

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#### Enhancing Post-Market Safety Monitoring and Surveillance

Once a drug is released onto the market for use by a patient group that includes those not represented in clinical trials, the safety picture may change. The use of medicines over longer time periods by a wider population can lead to adverse effects not seen in the clinical-trial population (such as was the case with Vioxx).<sup>68</sup> The FDA’s Sentinel initiative is a national electronic system that has transformed the way researchers monitor the safety of FDA-regulated medical products, including drugs, vaccines, biologics, and medical devices.<sup>69</sup> User fees generated by PDUFA will advance post-marketing drug safety evaluation through expansion of the Sentinel system and integration into FDA pharmacovigilance activities, and ensure timely and effective evaluation and communication of post-marketing safety findings related to human drugs.<sup>70</sup> In short, this matters because PDUFA VI will increase resources for the Sentinel program, helping facilitate post-marketing surveillance and ensuring that approved drugs remain safe as they broaden their reach throughout patient populations.

#### Enhancing FDA Workload and Workforce Planning

PDUFA VI will continue to enhance the FDA’s human drug review activities by enabling effective program and workload management and ensuring the FDA possesses the needed resources to support utilization of 21st-century regulatory science and approaches. In particular, financial-management enhancements in PDUFA VI will ensure the program remains on a stable, sustainable footing and facilitate more strategic program planning and

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management. For instance, the FDA’s Commitments Letter for PDUFA VI notes that the agency will “contract with an independent third party to conduct an evaluation of PDUFA program resource management during FY 2018 to ensure that PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner” and commits the agency “to publish a PDUFA 5-year financial plan no later than the 2nd quarter of FY 2018.”<sup>71</sup>

Likewise, PDUFA VI will assist the FDA with hiring and workforce management provisions, ensuring that the agency can recruit, train, and maintain the highest-quality medical and technical professionals with the advanced skills needed to undertake complicated human drug reviews. Specifically, as part of PDUFA VI, the FDA intends to complete development of position management baseline accounting of all current positions and full-time employee (FTE) counts engaged in the human drug review program for each applicable center and office; complete implementation of an online position classification system; complete establishment of a dedicated function to ensure needed scientific staffing for the human drug review program; and set clear goals for human drug review program hiring.<sup>72</sup>

Throughout the five iterations of PDUFA, its contributions in terms of helping the FDA effectively manage its workload and workforce, in addition to implementing effective project-management practices, has been among the program’s most important effects. However, challenges remain, making these provisions of PDUFA VI all the more important. As a 2015 presentation by John K. Jenkins, Director of the Office of New Drugs at the Center for Drug Evaluation and Research, noted, “the federal hiring system, Department of Health and Human Services (HHS) pay caps, and an outdated GS pay system, etc. continue to adversely impact our ability to recruit and retain the highly trained staff [the agency] needs to do our important public health work.”<sup>73</sup>

Although the impact on PDUFA-funded positions is not clear at this time, it’s also worth noting that, on January 23, 2017, President Trump issued an immediate hiring freeze that has the potential to affect many federal agencies, including the Food and Drug Administration and the National Institutes of Health. The hiring freeze may preclude the FDA from hiring needed medical and technical professionals with the skills required for reviewing drug applications and so has the potential to impede innovation and slow the development of treatments and cures for patients. Accordingly, the FDA should be treated as an exempted agency fulfilling a vitally important public-health mission.

## **RESPONDING TO CRITICISMS OF PDUFA**

Despite PDUFA’s extraordinary success, some have levied criticisms against the program. This section rebuts several of these critiques.

**Criticism 1: A failure to reauthorize PDUFA would simply mean longer wait times for drug reviews and determinations.**

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A failure to reauthorize PDUFA would have far more serious consequences than merely delaying drug review times. PDUFA is a bedrock component of the framework that supports medical research and discovery in the United States. PDUFA brings structure and stability by ensuring that the drug-review process incorporates the best practices and latest discoveries in regulatory science and that drug reviews proceed in a timely and efficient manner. If innovators didn't have that predictability, the rate of innovation would slow and fewer new drugs would come under development. For drugs that are currently in the development pipeline, PDUFA's absence would mean that funding for Phase 2 review meetings would be eliminated, so there would be far fewer drugs entering Phase 3 clinical trials. PDUFA VI also intends to increase the FDA's capacity for safety oversight in post-market surveillance by \$50 million, but this greater funding for post-market surveillance would be lost (ironically, decreasing the agency's ability to ensure drug safety for American citizens).

In the worst-case scenario, a congressional failure to reauthorize PDUFA in a timely manner could lead to the FDA having to issue reduction-in-force (RIF) notices, informing FDA employees whose positions are funded by PDUFA-collected fees that they are at risk of termination. This could have tremendously deleterious effects, including disruption of current drug reviews, potential loss of key staff, and future difficulty for the agency in attracting the highest-quality personnel. In short, a failure to reauthorize PDUFA would considerably hamstring the pharmaceutical research and development ecosystem in the United States and have far more serious consequences than simply longer decision periods for novel drug applications.

### **Criticism 2: PDUFA exposes the FDA to regulatory capture.**

Some have argued that PDUFA has caused the FDA to view the biopharmaceutical industry as a "partner" and source of revenue, rather as an industry over which the FDA has regulatory oversight.<sup>74</sup> But what critics miss is that PDUFA isn't about getting drug approvals in a timely manner; it's about making determinations regarding drug applications in a timely manner, and ensuring that only safe, effective medicines are brought to market. Consider cancer research. From 1998 to 2014, 103 attempts to develop melanoma drugs resulted in 7 new drugs but 96 unsuccessful attempts; 78 attempts to develop brain cancer drugs led to 3 new drugs and 75 unsuccessful efforts; and 177 attempts to develop new treatments for lung cancer led to 10 new drugs among 167 unsuccessful attempts.<sup>75</sup> In fact, less than 12 percent of the candidate medicines that make it into Phase I clinical trials are approved by the FDA, which is actually half the rate of a decade ago.<sup>76</sup> Drug approval is difficult; it is only given to pharmaceutical companies when they can sufficiently demonstrate their new drug compound displays superior benefits over risks in a specific population and for a specific indication.<sup>77</sup> If PDUFA somehow placed the FDA "in the pocket of industry," the percentages would be going the other way; the FDA would be approving many more drugs. If anything, the low drug-approval rates show just how difficult it is to create new medicines to cure near-intractable diseases at the frontiers of medical science.

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### Criticism 3: PDUFA turns the FDA from “regulator” to “partner” of the biopharmaceutical industry.

As noted, over the five iterations of PDUFA, the program has set up a robust series of interactions between the applicants and the FDA to facilitate information exchange as drug development moves from the preclinical phase into Phase 1, Phase 2, and Phase 3 clinical trials. For example, PDUFA provided funding for meetings as part of the scientific review at the conclusion of Phase 2 clinical trials between applicants and the FDA so that applicants have sufficient opportunity to ask questions and understand expectations for success as they move into Phase 3 of the clinical trials. Yet some have suggested that these types of meetings are too “cozy,” that they represent too much of a “partnership” on the part of the FDA in the drug-development process. But that misreads the intent of such meetings—to promote the exchange of information and to set expectations. Moreover, as ITIF has written, America’s regulators (whether reviewing drugs or autonomous vehicle technologies, for example) should not merely regard their role as regulating and evaluating the technologies that show up on their doorstep, but should work to enable and to accelerate the development of technologies that can contribute to realizing the agency’s core objectives. For example, for the National Highway Transportation Safety Administration (NHTSA), the goal is reducing traffic accidents and fatalities, and for the FDA it’s assuring that safe and effective drugs are brought forward that can help patients confront the medical illnesses and diseases they face.<sup>78</sup> This is also why PDUFA has significantly increased funding for post-market surveillance of drugs: to facilitate the FDA’s role in ensuring that drugs continue to be safe as they work their way through patient populations. The broader point here is that the FDA should indeed have an interest in seeing innovators develop new cures to diseases currently unsolved by medical science.

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*America’s regulators should not merely regard their role as regulating and evaluating the technologies that show up on their doorstep, but should work to enable and to accelerate the development of technologies that can contribute to realizing the agency’s core objectives.*

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Richard Williams of the Mercatus Center at George Mason University actually logs an opposite complaint from those who contend PDUFA makes the FDA too close to industry. He contends, “Congress continues to increase funding for FDA through both the general fund and industry user fees with the hope that performance goals and additional funding would increase FDA’s performance and lead to an increase in innovation. ... but the FDA finds strategic ways to narrowly meet each goal while frustrating the original goal of improving health outcomes through innovation.”<sup>79</sup> He argues here that the FDA’s processes aren’t enabling enough novel biomedical innovation. But in fact, these are the precise issues PDUFA VI has been designed to address. As noted, PDUFA VI helps put in place the structures—innovative new clinical-trial designs that support regulatory science, the incorporation of real-world medical evidence, meetings that help applicants better understand findings from FDA scientific reviews, etc.—that can help medical innovation flourish while still adhering to the FDA’s duty to ensure that only safe, effective drugs are brought to market. Moreover, if the FDA were frustrating the goal of improving health outcomes through innovation, why would industry continue to support the program?

It should also be noted that an impetus for Congress creating PDUFA in the early-1990s was the AIDS epidemic, when patient groups and pharmaceutical innovators alike were

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frustrated with long review periods and demanded faster review timeframes. AIDS activist groups such as ACT UP! even staged protests lamenting the slow process of drug approval and demanding that new drugs be reviewed as quickly as possible.<sup>80</sup> So, from its beginning, PDUFA was specifically intended as a collaboration between Congress, administrative regulators, and industry to shorten drug review times while maintaining the highest safety standards.

#### **Criticism 4: Swifter FDA approvals have caused more drug-safety problems.**

Some have contended that the accelerated drug-review timelines at the FDA have led the agency to approve more dangerous drugs. As Cassie Frank, lead author of the paper, “Era of Faster FDA Drug Approval Has Also Seen Increased Black-Box Warnings and Market Withdrawals” contends:

The FDA is under constant pressure to rush new drugs through the pipeline to approval. In its hurry, the FDA is apparently failing to distinguish useful drugs from toxic ones, and more dangerous drugs are slipping through. By the time many drugs receive serious safety warnings, millions of Americans have already been exposed to their side effects, which can sometimes be fatal.<sup>81</sup>

The authors, who examined 748 new drugs approved from 1975 through 2009, concluded that drugs approved after PDUFA’s passage were more likely to receive a new “black-box warning” or be withdrawn than drugs approved before its passage.<sup>82</sup> But as John Graham of the National Center for Policy Analysis notes, the study was rife with analytical errors and “an objective consideration of their analysis leads to a contrary conclusion.”<sup>83</sup> In particular, the authors mixed black-box warnings with withdrawals (and black-box warnings are a different outcome than withdrawals), and they reported their statistical results as percentages instead of raw figures. A withdrawal signals that a medicine shouldn’t have been allowed on the market, but a “black-box warning” (the FDA’s most stringent labeling requirement) informs users the drug may have severe side effects, meaning that new information has been discovered that can assist physicians in prescribing the medicine more appropriately.<sup>84</sup> As Graham notes, “This new information would not have been learned if the drugs had not been on the market.”<sup>85</sup> Second, reporting the statistical results as percentages, instead of absolute figures, omitted the fact that “there were actually more black-box warnings and withdrawals in the pre-PDUFA 16-year sample than the post-PDUFA 16-year sample: 80 versus 76.”<sup>86</sup> As Graham continues, in the pre-PDUFA sample, there were 68 warnings (on 42 drugs) and 12 withdrawals, while in the post-PDUFA sample, there were 58 warnings (on 48 drugs) and 18 withdrawals. And while that’s a higher number, “there were so few withdrawals that this comparison has no statistical power.”<sup>87</sup> And as Yevgeniy Feyman of the Manhattan Institute for Policy Research adds, “The authors identify a significant difference in black box warnings between the pre- and-post-PDUFA eras but make no serious attempt to control for other factors

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(including drug indications) which can significantly influence the observed rates of adverse effects over time.”<sup>88</sup>

Finally, even the study’s authors “acknowledge that they could not determine that the law [PDUFA] actually was the reason for increased safety problems.”<sup>89</sup> In other words, “they could not establish a causal relationship between the enactment of PDUFA and the [slightly] higher rates of black box warnings and withdrawals.”<sup>90</sup> Despite otherwise sensationalist headlines, they failed to link PDUFA to drug-safety issues. Rather, the authors simply speculate that approvals imposed by PDUFA deadlines may have rushed the FDA.<sup>91</sup> Ultimately, as Feyman concludes, “a flawed methodology and misrepresentation of the user-fee legal framework makes their conclusions indefensible and misleading.”<sup>92</sup>

**Criticism 5: Industry contributing to the financial cost of the agency reviewing it constitutes an unusual structure in the federal government.**

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*User fees send a signal that helps government agencies match demand with supply in the provision of citizen- or constituent-services and, if anything, should be more commonly used across the federal government.*

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Actually, the approach is quite standard across the federal government. In the health sector, Congress has also chartered the Medical Device User Fee Act (MDUFA) and the Generic Drug User Fee Amendments (GDUFA). Moreover, user fees are collected by many other agencies across the federal government. For instance, the U.S. Patent and Trademark Office (USPTO) is a 100 percent-user fee funded agency.<sup>93</sup> Industry and individuals pay application fees when they file for patent registrations, and the USPTO uses these proceeds to finance operations and the skilled experts needed to complete high-quality patent examinations. And, from 1996 to 2005, the USPTO approved just 55.8 percent of the 2.15 million new patent applications received.<sup>94</sup> Moreover, “the success rate of applications decreased substantially from 1996 to 2005, particularly for applications in the “drugs and medical instruments” and “computers and communications” fields. This hardly represents the picture of a government agency “captured” or “compromised” by the fees it receives from users.

Elsewhere in the government, the U.S. Air Traffic Control System is financed principally from fees collected from users of that system, mostly major U.S. airlines, and few would argue that the United States operates one of, if not the, world’s safest air-control systems. As the U.S. GAO found in a study of user fees applied across a wide variety of government agencies, “User fees can be designed to reduce the burden on taxpayers to finance the portions of activities that provide benefits to identifiable users above and beyond what is normally provided to the public. By charging the costs of those programs or activities to beneficiaries, user fees can also promote economic efficiency and equity.”<sup>95</sup>

If anything, the federal government should make greater use of these fees, because government agencies funded only by general (appropriations) funds tend to be characterized by chronic delays. That’s why, for instance, the average wait time for a veteran’s full mental-health evaluation is 26 days after an initial request (and as many as 279 days), and on average, the first treatment after full mental-health evaluation ranged from 1 to as many as 57 days.<sup>96</sup> In terms of veterans needing outpatient medical care, 21 percent of consults weren’t reviewed within 7 days, and 81 percent of follow-up care was

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provided after 90 days.<sup>97</sup> Likewise, wait times to receive green cards, passports, and visas can be inordinately long. For instance, nonimmigrant visa interview wait times for individuals from countries such as Brazil, India, and Mexico were in excess of 90 days, and up to 143 days before 2010. Likewise, when the USPTO was contending with fee diversion, patent backlogs stretched as long as four years. In short, wherever possible within the federal government, it's important to let demand signals get through, so they can help government agencies understand the supply they need to provide. User fees are a model to be emulated and expanded throughout the federal government.

## **CONCLUSION**

In conclusion, a timely reauthorization of PDUFA is critical to ensure that America's biopharmaceutical industry can continue to innovate and develop new treatments to help patients live healthier lives.<sup>98</sup> The Prescription Drug User Fee Act has played an instrumental role in ensuring the FDA has the necessary personnel and resources at its disposal to make safe, effective, and timely determinations regarding drug applications. Going forward, PDUFA VI will enable the FDA to incorporate the latest, 21st-century techniques in regulatory science to the process of drug development and review. PDUFA is a significant part of the reason why the FDA leads peer agencies in the timeliness of drug-application determinations and is widely recognized as one of the best drug-regulatory agencies in the world. Moreover, PDUFA provides a core pillar in a supportive policy framework—alongside robust public-private R&D investments and strong intellectual property rights protections—that have turned the United States from a laggard in the 1970s and 1980s into the world's leader in life-sciences innovation today. PDUFA VI represents the best of the public and private sectors working in concert to promote innovation and timely patient access to medicines in a safe and responsible way. Congress and the Trump administration should look favorably upon PDUFA VI reauthorization and move swiftly to reauthorize the program in 2017.

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