

October 28, 2021,

Dockets Management Staff (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Docket No. FDA-2021-N-0891; Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments**

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (“PhRMA”) is pleased to submit these comments on the Food and Drug Administration’s (“FDA” or “the Agency”) request for comments on proposed recommendations for the reauthorization of the Prescription Drug User Fee Act (“PDUFA”) for fiscal years (“FYs”) 2023 through 2027. PhRMA commends FDA for holding the virtual meeting to hear stakeholder views on PDUFA reauthorization.

PhRMA represents the country’s leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested more than \$1 trillion in the search for new treatments and cures, including an estimated \$91.1 billion in 2020 alone.<sup>1</sup>

PhRMA has been a strong supporter of, and participant in, PDUFA since its inception in 1992. We appreciate the opportunity to provide the following comments on the reauthorization of the PDUFA program<sup>2</sup> and strongly support the draft PDUFA VII commitment letter.

**I. PDUFA HAS BEEN A SUCCESS FOR FDA, INDUSTRY, AND PATIENTS**

In large part because of PDUFA, the United States now leads the world in the introduction of new medicines,<sup>3</sup> and the FDA’s human drug review program is the global gold standard for regulatory review and approval. Since 1992 when the program was enacted, PDUFA has provided more timely access to more than 1,700 new drugs and biologics including treatments for cancer, rare diseases, cardiovascular, neurological, and infectious diseases.

PDUFA continues to play an important role in strengthening the FDA’s ability to review human drug applications. The program also provides biopharmaceutical companies

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<sup>1</sup> PhRMA, “PhRMA 2020 Annual Membership Survey,” (2021), [https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/M-O/PhRMA\\_membership-survey\\_2021.pdf](https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/M-O/PhRMA_membership-survey_2021.pdf).

<sup>2</sup> Reauthorization of the Prescription Drug User Fee Act; Public Meeting; 86 FR 47316 (August 24, 2021).

<sup>3</sup> See U.S. Food and Drug Administration [hereinafter FDA], Center for Drug Evaluation and Research, “Advancing Health Through Innovation: New Drug Therapy Approvals 2020,” (January 2021), at 24, <https://www.fda.gov/media/144982/download>.

with greater regulatory predictability, which fosters industry investment in research and development.

## **II. PDUFA VII WILL ADVANCE INNOVATIVE RESEARCH AND DEVELOPMENT AND REVIEW APPROACHES TO PREPARE FOR THE FUTURE OF DRUG DEVELOPMENT**

Through the targeted improvements outlined in the draft PDUFA VII commitment letter,<sup>4</sup> the PDUFA VII agreement will have a lasting and meaningful impact on the biopharmaceutical industry's ability to develop innovative, safe, and effective medicines for patients. These improvements also leverage lessons learned in adapting to and meeting the challenges presented by the COVID-19 pandemic.<sup>5</sup> FDA and the biopharmaceutical industry are utilizing novel approaches to clinical trials and facility inspections to support continued innovation and inform efficient regulatory decision-making to address COVID-19. PDUFA VII includes commitments that advance COVID-19 lessons learned, such as increased use of digital technologies and alternative tools to assess manufacturing facilities.

### **1. PDUFA VII Will Strengthen Scientific Dialogue and Advance Innovation**

Effective interactions with FDA throughout development, from the pre-investigational new drug (IND) to the clinical development phase, can help minimize the risk of late-stage drug development failures, increase the probability that safety and efficacy data are available in a timely manner, and mitigate issues that would delay patient access to approved treatments.

PDUFA VII proposed performance goals will expand opportunities for obtaining FDA feedback throughout the drug development process through formalized Initial Targeted Engagement for Regulatory Advice on CDER/CBER Products (INTERACT) meetings for innovative products early in development.<sup>6</sup> PDUFA VII will also enable creation of a new formal Type D meeting<sup>7</sup> with a shorter timeframe for focused discussion, including on innovative approaches, and enhanced processes and timelines for communicating and reviewing post-marketing requirements.

PDUFA VII proposed performance goals also include new and enhanced procedures, timelines and guidance for human factor validation protocols and use-related risk analysis for combination products.<sup>8</sup> In addition, PDUFA VII will establish new pilot programs for supporting efficacy endpoint development for rare diseases and Split Real Time Application Review (STAR) to shorten time to the action date for certain novel uses of approved therapies.<sup>9</sup> Streamlined processes and prompt FDA feedback on sponsor questions and pressing development issues will help ensure regulatory efficiency and predictability for drug development programs involving innovative approaches.

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<sup>4</sup> FDA, "PDUFA Reauthorization Performance Goals and Procedures Fiscal years 2023 Through 2027," [hereinafter "PDUFA VII Commitment Letter"], <https://www.fda.gov/media/151712/download>.

<sup>5</sup> See PDUFA VII Commitment Letter at 28.

<sup>6</sup> *Id.* at 21-22.

<sup>7</sup> *Id.* at 21.

<sup>8</sup> *Id.* at 34-35.

<sup>9</sup> *Id.* at 14-17, 30-34.

## **2. PDUFA VII Will Enhance Patient-Centric Drug Review and Safety Monitoring**

Through the Patient-Focused Drug Development (PFDD) Initiative established as part of PDUFA V<sup>10</sup> and continued in PDUFA VI,<sup>11</sup> FDA has gained a better understanding of the disease, condition, and treatment elements that are of greatest importance to patients. PDUFA VI also provided significant resources to support the Agency's ability to review, track, and communicate important post-market safety information. This included an investment to expand the Sentinel System's capabilities and enhance the communication process with stakeholders on the use of Sentinel data.<sup>12</sup>

PDUFA VII proposed performance goals will build on initiatives from PDUFA V and VI and advance the incorporation of patient-centric data into drug development and regulatory reviews. Enabling further incorporation of the patient perspective, including through guidance on patient preference information, and expanded FDA staff training and outreach, will help enhance the patient-centric process by which the industry develops new medicines that address the needs of patients.

Implementation of the proposed PDUFA VII performance goals will also improve Risk Evaluation and Mitigation Strategies (REMS) assessments and advance Sentinel capabilities. Specifically, PDUFA VII will establish new timelines for FDA review of methodological approaches and study protocols for REMS assessments.<sup>13</sup> PDUFA VII will also advance the Sentinel analytical capabilities to support the use of Sentinel to address questions of product safety and address how real-world evidence (RWE) can be used for studying a drug's effectiveness.<sup>14</sup>

In addition, to support implementation of a standardized process for determining necessity and type of pregnancy postmarketing studies, PDUFA VII includes new Sentinel demonstration projects for assessing pregnancy outcomes in women exposed to drugs and biological products.<sup>15</sup>

## **3. PDUFA VII Will Support the Next Wave of Advanced Biological Therapies**

A significant area of focus in modern drug development is the field of cell and gene therapy, which involves the delivery of targeted cells or genetic material into patients. Gene therapy research holds tremendous promise in leading to the possible development of highly specialized treatments for patients with a variety of conditions, including genetic diseases, cancer, and infectious disease.

Implementation of the proposed PDUFA VII performance goals will help ensure the efficient review of applications and timely patient access to innovative biological therapies regulated by FDA's Center for Biologics Evaluation and Research (CBER), including cell and gene therapies. Specifically, FDA will issue guidance on the use of expedited programs for

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<sup>10</sup> See FDA "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017," [hereinafter "PDUFA V Commitment Letter"] at 22, 24-25, <https://www.fda.gov/media/81306/download>.

<sup>11</sup> See FDA, "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022," [hereinafter "PDUFA VI Commitment Letter"] at 27-30, <https://www.fda.gov/media/99140/download>.

<sup>12</sup> *Id.* at 34-36.

<sup>13</sup> See PDUFA VII Commitment Letter at 43, 44.

<sup>14</sup> *Id.* at 44-45, 47.

<sup>15</sup> *Id.* at 46-47.

regenerative medicines, improve communication best practices, facilitate review of manufacturing information for products with accelerated clinical development, and advance PFDD activities.<sup>16</sup> PDUFA VII also includes a public process to discuss ways cell and gene therapy manufacturers can appropriately leverage a sponsor's internal prior knowledge and public knowledge across therapeutic areas to facilitate development and review of cell and gene therapies.<sup>17</sup>

Implementation of the proposed PDUFA VII performance goals will also help enable broader use of novel trial designs and approaches for small patient populations and evaluate their application to more common diseases.<sup>18</sup> CBER will be provided dedicated resources to facilitate necessary hiring and training reviewers for these transformative therapies.

#### **4. PDUFA VII Will Modernize Regulatory Evidence Generation and Drug Development Tools**

Delivering new medicines to patients through biomedical innovation requires advancing the development and application of the latest regulatory science approaches to drug development. New and powerful tools emphasize individual patient characteristics and include complex innovative clinical trial designs, the use of RWE, patient-reported outcomes, and advanced statistical methods. PDUFA VII will further modernize regulatory evidence generation and increase transparency and promote stakeholder learning around acceptable uses of innovative approaches for regulatory decision-making.

PDUFA VII will establish a new pilot program to advance the use of RWE for regulatory decision-making, including for approval of new indications or to satisfy postmarketing study requirements, holding public workshops, and issuing guidance documents on the use of RWE.<sup>19</sup> Proposed PDUFA VII performance goals will also facilitate greater use of innovative clinical trial designs by advancing the use of complex adaptive and other novel clinical trial designs, including guidance on Bayesian approaches, and continuing the complex innovative trial design pilot put in place as part of the PDUFA VI commitments.<sup>20</sup> PDUFA VII will also further advance consistency and predictability around the use of modeling and simulations, including model-informed drug development (MIDD) approaches, in regulatory decision-making.<sup>21</sup>

#### **5. PDUFA VII Will Advance Digital Health Technologies and Information Technology (IT) Infrastructure**

An efficient and predictable regulatory review process depends on a supportive technology infrastructure. Data and technology modernization is necessary to support initiatives such as cloud-based technology and requires a strategic approach that is transparent and promotes active collaboration with stakeholders. Digital health technologies (DHTs) – such as digital health products, artificial intelligence, and machine learning – present significant opportunities to support clinical trials and decentralized clinical trials.

The PDUFA VII proposed performance goals will help establish a robust and efficient framework to facilitate the adoption of innovative digital health products, as well as promote

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<sup>16</sup> See PDUFA VII Commitment Letter at 53-56.

<sup>17</sup> *Id.* at 56.

<sup>18</sup> *Id.* at 54-55.

<sup>19</sup> *Id.* at 36-38, 47, 55.

<sup>20</sup> *Id.* at 41-42.

<sup>21</sup> *Id.* at 40-41.

coordination and utilization of DHTs in regulatory decision-making across FDA.<sup>22</sup> Public workshops and guidance will address issues related to the use of DHTs in regulatory decision-making, including the potential for DHTs to increase diverse patient populations in clinical trials.<sup>23</sup> PDUFA VII initiatives will also modernize FDA's data and IT capacity and capabilities, including adoption of cloud-based technologies, enhanced support for the review of DHT-generated data, and increased bioinformatics and computational biology capacity to enable review of complex biological data, such as Next Generation Sequencing.<sup>24</sup>

## **6. PDUFA VII Will Enhance Innovation in Manufacturing and Product Quality Reviews**

Manufacturing and quality play a vital role in the drug development process and ensuring timely patient access to innovative medicines. In each reauthorization of PDUFA, FDA and industry have further defined the review process for marketing applications to ensure that the Agency's review remains on track and allows applicants visibility into FDA's review for purposes of increasing first cycle approvals for those applications that are approved by FDA. Enhanced communications on Chemistry, Manufacturing, and Controls (CMC) during drug development and application review will provide sponsors even greater regulatory predictability.

Implementation of the proposed PDUFA VII performance goals will help promote a more efficient review process and advance the use of innovative manufacturing technologies across product platforms and manufacturing sites.<sup>25</sup> This will help facilitate innovation in manufacturing processes and clear communication between sponsors and the FDA during the drug review process. In addition, PDUFA VII will establish a new pilot to facilitate CMC readiness for products with accelerated clinical development timelines.<sup>26</sup> PDUFA VII goals also includes a commitment for FDA to issue guidance on the use of alternative tools to assess manufacturing facilities named in pending applications, including incorporation of best practices from the use of such tools during the COVID-19 pandemic.<sup>27</sup>

## **7. PDUFA VII Will Build on PDUFA VI Efforts to Modernize FDA Financial and Staff Resource Management**

PDUFA VI included improvements to the financial structure of the PDUFA program<sup>28</sup> aimed to help ensure financial stability and appropriate staffing for the FDA to meet negotiated goals, with implementation and maturation of these reforms expected to continue into PDUFA VII. PDUFA VI also included improvements to the hiring process and set goals for the hiring of new staff that was needed to fulfill the human drug review program mission.

PDUFA VII proposed performance goals will build on the foundational work started in PDUFA VI to help improve accountability and transparency and modernize financial and staff resource management. PDUFA VII proposed performance goals will also help ensure that FDA has adequate staffing through improvements to recruitment, hiring, retention, and training.<sup>29</sup>

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<sup>22</sup> See PDUFA VII Commitment Letter at 64-67.

<sup>23</sup> *Id.* at 65-67.

<sup>24</sup> *Id.* at 60-64, 67-68.

<sup>25</sup> *Id.* at 48-53.

<sup>26</sup> *Id.* at 50-52.

<sup>27</sup> *Id.* at 49-50.

<sup>28</sup> See PDUFA VI Commitment Letter at 37-41.

<sup>29</sup> See PDUFA VII Commitment Letter at 57-59.

### III. CONCLUSION

As drafted, the draft PDUFA VII commitment letter will help advance an effective, science-based regulatory review program that helps ensure that biopharmaceutical companies continue to bring innovative medicines to patients in need. PhRMA fully supports both the proposed PDUFA VII performance goals as well as the legislative reauthorization of PDUFA. We look forward to working with FDA, Congress, patient and medical provider groups, and other stakeholders to ensure timely reauthorization of this important program.

Respectfully submitted,

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