



October 28, 2021

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

**Re: Docket No. FDA-2021-N-0891: “Reauthorization of the Prescription Drug User Fee Act”**

Dear Sir or Madam:

Thank you for the opportunity to submit comments on behalf of the National Organization for Rare Disorders, or NORD, regarding the Food and Drug Administration (FDA) Public Meeting, *Reauthorization of the Prescription Drug User Fee Act*. Founded in 1983, NORD represents 328 different rare disease patient organizations and the 25-30 million Americans living with a rare disease. We are committed to identifying, treating, and curing rare disorders through programs of education, advocacy, research, and patient services. It is on behalf of our member organizations and the broader rare disease community that we write to you today.

NORD appreciates the efforts of the FDA and negotiating parties in advancing a strong Prescription Drug User Fee Act (PDUFA) VII Commitment Letter (Commitment Letter).<sup>1</sup> We believe that many of the commitments will improve the development and review of drugs for rare diseases. Despite the significant progress made possible by the passage of the 1983 Orphan Drug Act and previous PDUFA agreements, rare diseases remain an area with significant unmet need. Over 90% of rare diseases still do not have an FDA-approved treatment indicated for their specific rare disease. Therefore, we support the approaches outlined in this Commitment Letter to facilitate drug development, as well as timely review by FDA to ensure more treatment options are available to address the needs of rare disease patients.

Since its inception, FDA’s user fee programs have enabled FDA to conduct more efficient and timely reviews, while maintaining the Agency’s gold standard. NORD applauds FDA for fulfilling many of the PDUFA VI commitments relating to rare diseases.<sup>2</sup> FDA has held public workshops, issued guidance, and advanced reviewer training to aid in rare disease drug reviews. FDA also fulfilled other commitments that advance rare disease drug development, including publishing guidance on patient-focused drug development (PFDD), promoting the use of real-world evidence (RWE), and enhancing reporting requirements to educate the public on rare

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<sup>1</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. (2021). Accessed 10/15/21. <https://www.fda.gov/media/151712/download>

<sup>2</sup> FDA. FY 2020 Performance Report to Congress. Accessed 10/26/21. <https://www.fda.gov/media/151602/download>

disease activities.<sup>3</sup> NORD is pleased to see a continued commitment to rare diseases in the PDUFA VII Commitment Letter.

NORD is grateful to be a part of the PDUFA VII reauthorization process and to have had the opportunity to provide our input. At the outset of the PDUFA VII reauthorization process, NORD urged FDA and its negotiating partners to include four priorities in the reauthorization of PDUFA VII:

- 1) Ensure that the Center for Biologics Evaluation and Research (CBER) has the resources to match its critical responsibilities;
- 2) Incorporate the ongoing work in Rare Disease Cures Accelerator (RDCA) program into the reauthorization of PDUFA;
- 3) Build on the success of FDA's PFDD efforts; and
- 4) Continue to incorporate the learnings from the pandemic into the drug development process.

The Commitment Letter addresses these and many other goals that will significantly advance rare disease drug development and benefit the rare disease community. NORD appreciates the opportunity to provide the following comments on the Commitment Letter.

#### Advancing Drug Development for Rare Diseases in PDUFA VII

NORD applauds the Commitment Letter's focus on the advancement of drug development for rare diseases. CBER and CDER have committed to continuing the integration of rare disease staff into review divisions to ensure rare disease expertise is optimized throughout the review process. NORD believes this is a critical and constructive step. Rare diseases impact every system and part of the body, which means that any review division at the FDA may consider a rare disease application. Rare disease drug applications are often complex due to data collection challenges stemming from small patient populations. Additionally, the review of applications that rely on innovative methods to demonstrate the safety and effectiveness in rare disease drug development, such as the use of novel endpoints, adaptive study designs, and new methodologies for statistical analysis, requires the unique and collaborative approach envisioned in the Commitment Letter.

NORD is also encouraged that FDA has committed to incorporating rare disease training into the core curriculum for reviewers. Rare disease drug development poses unique challenges, such as small, heterogeneous patient populations and limited or non-existent natural history data, all of

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<sup>3</sup> Ibid.

which can make endpoint selection difficult.<sup>4,5</sup> Training that focuses on these challenges can help reviewers understand these applications, utilize regulatory flexibility as appropriate, and foster confidence in their ability to review rare disease products. Additionally, training can help to ensure that reviews are consistent across review divisions.

NORD also applauds the Commitment Letter's focus on engagement with external stakeholders to educate them about rare disease programs at FDA. Ensuring that the rare disease community understands the ongoing efforts at the FDA to advance rare disease drug development is an important step in helping bring the community together to support FDA and industry partners.

### *Rare Disease Endpoint Accelerator Pilot Program*

The Rare Disease Endpoint Accelerator (RDEA) Pilot Program will provide critical resources to address novel endpoint development, a long-standing obstacle for rare disease drug development.<sup>6,7</sup> As noted in the Commitment Letter, establishing appropriate efficacy endpoints in rare diseases is often challenging because of a lack of regulatory precedent, small trial populations, and limited understanding of a disease's natural history.<sup>8</sup> The RDEA program will provide selected sponsors with an opportunity for earlier structured, repeated interactions with FDA to help in the evaluation and development of appropriate novel endpoints. In addition, NORD is pleased to see that FDA will consider the applicability of the endpoints for multiple diseases, which will help broaden the impact of the pilot beyond the selected applicants.<sup>9</sup> It is critical that the learnings from this program ultimately be made available so that future rare disease drug applications can build on the progress made within the program.

NORD believes that the success of the RDEA program can be bolstered by the work being conducted in the Rare Disease Cures Accelerator-Data Analytics Platform (RDCA-DAP). Led collaboratively by the Critical Path Institute and NORD, the RDCA-DAP is an FDA-funded project that will create a widely available data resource, through which researchers and

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<sup>4</sup> Golsmith, G., Kempf, L., Blumenrath, S. DIA. The Challenge of Rare Diseases – From Drug Development to Approval. Accessed 10/20/21. <https://globalforum.diaglobal.org/issue/april-2018/the-challenge-of-rare-diseases-from-drug-development-to-approval/>

<sup>5</sup> FDA. Rare Diseases: Common Issues in Drug Development Guidance for Industry. (2019). <https://www.fda.gov/media/119757/download>

<sup>6</sup> Raver, C, Valentine, J. FDA Law Blog. The FDA PDUFA VII Goals Letter (FY 2023-2027): A Review of Our Top 10 Commitments. Accessed 9/25/21. [https://www.thefdalawblog.com/2021/09/the-fda-pdufa-vii-goals-letter-fy-2023-2027-a-review-of-our-top-10-commitments/?utm\\_source=feedburner&utm\\_medium=feed&utm\\_campaign=Feed%3A+FdaLawBlog+%28FDA+Law+Blog%29](https://www.thefdalawblog.com/2021/09/the-fda-pdufa-vii-goals-letter-fy-2023-2027-a-review-of-our-top-10-commitments/?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+FdaLawBlog+%28FDA+Law+Blog%29)

<sup>7</sup> Pink Sheet. US FDA's Stein 'Excited' About Real-World Evidence, Rare Disease Endpoint Pilot Programs. Accessed 10/15/21. <https://pink.pharmaintelligence.informa.com/PS144943/US-FDAs-Stein-Excited-About-RealWorld-Evidence-Rare-Disease-Endpoint-Pilot-Programs>

<sup>8</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 30. (2021). Accessed 10/15/21. <https://www.fda.gov/media/151712/download>

<sup>9</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 31. (2021). Accessed 10/15/21. <https://www.fda.gov/media/151712/download>

drug developers can access and analyze de-identified, patient-level data on rare diseases, and how they progress, leading to new insights about those diseases. The RDCA-DAP can provide potential drug development sponsors, even prior to the start of their own clinical studies, with access to (otherwise very hard to obtain) patient-level, rare disease data, and associated statistical analysis tools, that will allow sponsors to develop better proposals for the design and endpoints of their rare disease clinical trials. In so doing, the discussions with FDA during the RDEA consultation process can be improved. NORD encourages both sponsors and FDA to make full use of this resource in the RDEA Pilot.

### Addressing CBER Resource Needs

In recent years, there has been a dramatic rise in the number of investigational new drugs (INDs) received at CBER, driven in large part by advancements in cell and gene therapies.<sup>10,11</sup> NORD applauds CBER for the proposed enhancements to the Cell and Gene Therapy Program (CGTP) in the Commitment Letter. Science and technology are evolving rapidly, and there is more opportunity than ever before to address the more than 7,000 monogenetic diseases that currently exist. Given that 80% of all rare diseases have a known monogenetic origin, the promise of gene therapy for the rare disease community cannot be overstated.<sup>12</sup> It is critical that CBER's resources match the demands that are currently being placed on it as the workload will only increase in years to come.

At the end of 2019, CBER had over 900 active IND applications.<sup>13</sup> Since 2018, CBER has received more than 200 INDs for cell and gene therapies alone per year.<sup>14</sup> Cell and gene therapy INDs more than doubled between 2016 and 2018, the first year with over 200 INDs for cell and gene therapies.<sup>15</sup> The onset of COVID-19 also resulted in a considerable expansion in workload for CBER.<sup>16</sup> Now, COVID-19 products, which had not been incorporated into previous estimates of CBER's workload,<sup>17</sup> have added to it dramatically. In Fiscal Year 2020, CBER received 6,575

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<sup>10</sup> Pink Sheet. Scientific Wave Pushes CBER Into Brighter Light. Accessed 10/1/21.

<https://pink.pharmaintelligence.informa.com/PS141927/Scientific-Wave-Pushes-CBER-Into-Brighter-Light>

<sup>11</sup> RAPS. CBER lays out volume-staff mismatch in PDUFA VII meetings. Accessed 10/15/21.

<https://www.raps.org/news-and-articles/news-articles/2021/1/cber-lays-out-volume-staff-mismatch-in-pdufa-vii-m>

<sup>12</sup> National Center for Advancing Translational Science. Gene Therapy Platform for Rare Diseases. Accessed 10/18/21. <https://ncats.nih.gov/trnd/projects/gene-therapy>

<sup>13</sup> Pink Sheet. Scientific Wave Pushes CBER Into Brighter Light. Accessed 9/20/21.

<https://pink.pharmaintelligence.informa.com/PS141927/Scientific-Wave-Pushes-CBER-Into-Brighter-Light>

<sup>14</sup> Ibid.

<sup>15</sup> Ibid.

<sup>16</sup> Pink Sheet. The COVID Boom: CBER Receives More INDs in One Quarter Than the Previous 30 Combined. (2021). Accessed 9/20/21. <https://pink.pharmaintelligence.informa.com/PS144122/The-COVID-Boom-CBER-Receives-More-INDs-in-One-Quarter-Than-The-Previous-30-Combined>

<sup>17</sup> MIT NEWDIGS. Projections from the existing pipeline of cell and gene therapies: Launches and patient numbers. (2018). <https://newdigs.mit.edu/sites/default/files/FoCUS%20Research%20Brief%20202018F210v027.pdf>

new INDs in 6 months.<sup>18</sup> Since then, CBER has been receiving close to 200 INDs (for all CBER-regulated products) per quarter in Fiscal Year 2021.<sup>19</sup> To realize the promise of gene therapies, it is critical that FDA can keep pace, both in the regulatory science and in its reviews of applications.

Under PDUFA VII, the 228 planned CBER hires<sup>20</sup> are a welcome increase of 196 more full-time employees (FTEs) than the 32 provided in PDUFA VI.<sup>21</sup> In the next two years, CBER estimates that as many as 100 staff will be needed to return to the pre-pandemic level of responsiveness.<sup>22</sup> As noted in the Commitment Letter, this increase in staffing will not only allow CBER to spend additional time on meetings with sponsors and review submissions but will also permit staff to engage in other equally important work, like policy and guidance development as well as working with external stakeholders.<sup>23</sup> Additional staff will also help with resource-intensive programs like Initial Targeted Engagement for Regulatory Advice on CBER/CDER Products (INTERACT), Breakthrough Therapy, and Regenerative Medicines Advanced Therapies (RMAT). These programs provide sponsors of qualifying products with critical opportunities for early and more frequent engagement with FDA review staff, leading to more efficient product development and review. We applaud this increase in staffing and urge FDA to move forward with hiring as expeditiously as possible.

However, CBER's needs go beyond new FTEs. The applications being submitted to CBER represent some of the most innovative technologies in the world, and their submissions can involve highly complex data sets. CBER needs the technological infrastructure to keep pace.<sup>24</sup> Therefore, NORD is pleased to see the Commitment Letter's focus on technology modernization at CBER which will allow for efficient review of data sets and enable smoother review of applications. Ensuring that CBER has both the staff and technological capacity to handle review is essential for patients to gain access to CBER-regulated products in a timely manner.

### *Review and Approval of Cell and Gene Therapies*

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<sup>18</sup> CBER. Number of Original Investigational New Drug (IND) applications received in the quarter. Accessed 9/20/21. <https://www.accessdata.fda.gov/scripts/FDA/Track/view/track.cfm?program=cber&id=CBER-All-IND-and-IDEs-recieved-and-actions>

<sup>19</sup> Ibid.

<sup>20</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 59. (2021). Accessed 9/17/21. <https://www.fda.gov/media/151712/download>

<sup>21</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022. (2017). Accessed 9/17/21. <https://www.fda.gov/media/99140/download>

<sup>22</sup> Pink Sheet. CBER Will Staff Up With 100 More Reviewers 'By Hook Or By Crook,' Marks Says. Accessed 9/27/21. <https://pink.pharmaintelligence.informa.com/PS144281/CBER-Will-Staff-Up-With-100-More-Reviewers-By-Hook-Or-By-Crook-Marks-Says>

<sup>23</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 53. (2021). Accessed 9/17/21. <https://www.fda.gov/media/151712/download>

<sup>24</sup> RAPS. CBER lays out volume-staff mismatch in PDUFA VII meetings. Accessed 10/15/21. <https://www.raps.org/news-and-articles/news-articles/2021/1/cber-lays-out-volume-staff-mismatch-in-pdufa-vii-m>

In addition to ensuring CBER's staffing and technological infrastructure needs are addressed, the Commitment Letter also focuses on the need for advancing regulatory science for cell and gene therapies, as well as patient-focused development around these products. Because of the relative newness of cell and gene therapies, there is a lack of understanding about these products among patients.<sup>25</sup> The last few years have brought headlines about groundbreaking curative gene therapies which has instilled hope in many rare disease patients. The patient-focused drug development meeting to be held by the end of Fiscal Year 2023 will be an important opportunity for FDA and patients alike to exchange information on cell and gene therapies, their benefits and risks, as well as helping patients understand how they can get involved in clinical development.<sup>26</sup>

In the Commitment Letter, FDA has outlined other public opportunities, such as guidance and public meetings, to advance the development of novel cell and gene therapies, including guidance on small patient populations, addressing the lack of natural history data, focusing on questions and answers to address common concerns, and using RWE to address postmarket safety and efficacy.<sup>27</sup> Additionally, NORD is pleased to see FDA's commitment to updating guidance for regenerative medicines that utilize expedited programs. Cell and gene therapies are rapidly evolving, and these commitments are needed to advance the development of these products and bring these innovative, groundbreaking treatments to patients.

#### Enhancements Related to Patient-Focused Drug Development Efforts

NORD appreciates that the Commitment Letter continues FDA's focus on incorporating the patient voice into the drug development and regulatory review processes. NORD has had the opportunity to assist in planning and conducting two externally-led PFDD meetings, including one on Polycystic Kidney Disease in September 2020 and on Krabbe Disease in October 2020. In conjunction with FDA's Patient Affairs Staff at FDA, NORD has jointly conducted 12 Patient Listening Sessions with review divisions across CBER and CDER on a variety of disease states. Shortly after the COVID-19 pandemic began, NORD conducted two special FDA listening sessions with the rare disease community at large regarding COVID-19. The first session with the Oncology Center of Excellence focused on rare cancers. The second, with CDER and CBER, focused on access to personal protective equipment, research and clinical trials, and concerns about drug shortages. NORD has worked to bring the patient community together for these meetings, and, as we have learned, both the patients and FDA benefit.

NORD welcomes provisions in the Commitment Letter to increase the utilization of PFDD, including the draft guidance on the use and submission of patient preference information for

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<sup>25</sup> PR Newswire. Research Reveals Lingering Misconceptions about Gene Therapy as Promising New Product Candidates Advance. Accessed 9/25/21. <https://www.prnewswire.com/news-releases/research-reveals-lingering-misconceptions-about-gene-therapy-as-promising-new-product-candidates-advance-300439670.html>

<sup>26</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 54. (2021). Accessed 9/17/21. <https://www.fda.gov/media/151712/download>

<sup>27</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 55. (2021). Accessed 9/17/21. <https://www.fda.gov/media/151712/download>

regulatory decision making.<sup>28</sup> Currently, patient data is inconsistently collected and can have limited value in regulatory decision making.<sup>29</sup> Changing this paradigm to ensure robust, fit-for-purpose patient data is consistently collected will increase the value and utility of patient data within the FDA review process.

Critical to the goal of patient-focused drug development is improving the availability of an appropriate Clinical Outcome Assessment (COA). COAs are important measures of how a patient feels, functions, or survives, which can serve as primary or secondary endpoints for a clinical study.<sup>30</sup> NORD supports FDA's commitments to developing a virtual catalog of COAs as well as holding a public meeting on the areas with the most need of COAs.<sup>31</sup> Developing COAs for rare diseases is especially challenging due to the heterogeneity of rare diseases and the lack of understanding of clinical manifestations or the natural history of rare diseases.<sup>32</sup> The development of these resources is a key priority for NORD.

NORD is currently involved in several efforts to establish and standardize COAs for clinical trial use. A second component in the RDCA program is aimed at developing COAs for rare diseases. NORD is also involved in this component and has partnered with the Critical Path Institute to develop the Rare Disease COA Consortium to create and curate a resource of information on publicly available COAs identified as potentially fit-for-purpose endpoint measures for rare disease clinical trials.<sup>33,34</sup> The Consortium seeks to bring different stakeholders together in the pre-competitive setting to address issues that exist with developing COAs. The Consortium hopes to identify best practices, identify the measures that are important to patients with rare diseases, and standardize how information is collected across different stakeholders, reducing the need for proprietary measures. NORD believes that engaging in a pre-competitive space to address these issues will lead to more collaboration among sponsors and optimize how studies using COAs are designed.

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<sup>28</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 38. (2021). Accessed 9/17/21. <https://www.fda.gov/media/151712/download>

<sup>29</sup> FDA. Assessment of the Use of Patient Experience Data in Regulatory Decision-Making. (2021). Accessed 10/20/21. <https://www.fda.gov/media/150405/download>

<sup>30</sup> FDA. Clinical Outcome Assessment (COA): Frequently Asked Questions. Accessed 10/12/21.

<https://www.fda.gov/about-fda/clinical-outcome-assessment-coa-frequently-asked-questions#Consideration1>

<sup>31</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 39. (2021). Accessed 9/17/21. <https://www.fda.gov/media/151712/download>

<sup>32</sup> Dashiell-Aje, E., Kovacs, S. Opportunities: A Regulatory Perspective on the Development of Suitable Clinical Outcome Assessments (COAs) for Rare Diseases. Accessed 10/20/21.

<https://globalforum.diaglobal.org/issue/august-2018/opportunities-a-regulatory-perspective-on-the-development-of-suitable-clinical-outcome-assessments-coas-for-rare-diseases/>

<sup>33</sup> Critical Path Institute. C-Path Receives FDA Grant to Establish Rare Disease Clinical Outcome Assessment Consortium. Accessed 10/28/21. <https://c-path.org/c-path-receives-fda-grant-to-establish-rare-disease-clinical-outcome-assessment-consortium/>

<sup>34</sup> Critical Path Institute. Establishment of the Rare Disease COA Consortium. Accessed 10/15/21. [https://c-path.org/wp-content/uploads/2021/03/2021\\_RareDisease\\_SC\\_Poster.pdf](https://c-path.org/wp-content/uploads/2021/03/2021_RareDisease_SC_Poster.pdf)

Additionally, NORD has partnered with Northwestern University Clinical Outcome Assessment Team (NUCOAT) to develop certain new COAs of physical function using both patient-reported and performance measurement outcomes, including mobility, physical activity, and activities of daily living.<sup>35,36</sup> This program is funded as part of CDER's Pilot Grant Program for COAs<sup>37</sup> within the larger PFDD initiative.<sup>38</sup> The NORD/NUCOAT program seeks to apply known COAs to certain rare disorders and common sarcopenia diseases to assess their applicability in clinical trials.<sup>39</sup> The result of this program will be the delivery of publicly available and accessible core clinical outcome sets for measuring physical function in clinical trials, with the potential for application across different conditions.<sup>40</sup> These COA efforts are important for patients as they seek to convert patient preferences into tools sponsors can use in drug development to demonstrate the clinical benefit of a treatment. Unfortunately, rare diseases can often be overlooked in COA development due to the small population size and substantial investment required for these activities. Therefore, NORD looks forward to FDA's continuing support of these two programs and finding further opportunities to develop COAs for rare diseases.

#### Advancing Drug Development Utilizing Lessons Learned from the COVID-19 Pandemic

Rare disease patients have been impacted by the COVID-19 pandemic in unique and difficult ways. Access to routine care became a safety risk for rare disease patients, particularly for those who are immunocompromised. Participation in clinical trials for rare disease patients similarly posed new threats. As a result, remote access to both ongoing care and clinical trial sites became critically important for the rare disease community. Patients with rare diseases often are faced with extremely limited options for care given the small number of specialists for their condition. Therefore, it is not uncommon for a rare disease patient to be forced to travel great distances to see a specialist<sup>41</sup> or to access a clinical trial site, which usually means taking time off work and incurring significant financial expenses. These challenges were amplified during COVID-19, as mass transit was scaled back, and many services, including medical appointments, came to a halt or required extra precautions.

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<sup>35</sup> NORD. Physical Function Clinical Outcome Assessments for Rare Disorders and Sarcopenia Planning Core Outcome Sets with FDA. Accessed 10/20/21. <https://rarediseases.org/event-posters/physical-function-clinical-outcome-assessments-for-rare-disorders-and-sarcopenia-planning-core-outcome-sets-with-fda/>

<sup>36</sup> Northwestern. NUCOAT. Accessed 10/18/21. <https://sites.northwestern.edu/nucoat/>

<sup>37</sup> FDA. CDER Pilot Grant Program: Standard Core Clinical Outcome Assessments (COAs) and their Related Endpoints. Accessed 10/15/21. <https://www.fda.gov/drugs/development-approval-process-drugs/cder-pilot-grant-program-standard-core-clinical-outcome-assessments-coas-and-their-related-endpoints>

<sup>38</sup> FDA. CDER Patient-Focused Drug Development. Accessed 10/20/21. <https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development>

<sup>39</sup> Northwestern. NUCOAT: Planning Phase. Accessed 10/18/21. <https://sites.northwestern.edu/nucoat/ug3/>

<sup>40</sup> Cella, D., Flores, A., et al. Northwestern University. Northwestern University Clinical Outcome Assessment Team (NUCOAT). Accessed 10/28/21. <https://www.scholars.northwestern.edu/en/projects/northwestern-university-clinical-outcome-assessment-team-nucoat-3>

<sup>41</sup> NORD. Ensuring Access to Telehealth for Rare Diseases. (2020). Accessed 9/15/21. <https://rarediseases.org/wp-content/uploads/2020/10/NRD-2098-RareInsights-Telehealth-Report-1.pdf>

The field of digital health has changed rapidly over the last 20 years and has been accompanied by challenges in terms of the ability to provide credible, high-quality data that can ultimately be used in regulatory decisions.<sup>42</sup> The COVID-19 pandemic has prompted an increased shift toward more remote monitoring and use of Digital Health Technologies (DHTs) that has allowed for a concomitant shift toward fully or partially decentralized clinical trials (DCTs) during the COVID-19 pandemic.<sup>43,44</sup> Minimizing the number of visits to a clinical trial site, while still capturing high-quality data for use in a clinical study, is an advancement that rare disease patients have sought for quite a long time.

FDA responded promptly to the pandemic and ensured that many patients involved in a clinical trial were able to continue their participation.<sup>45</sup> NORD commends the FDA for recognizing the advancements in DHTs and the potential for these technologies to improve patient experiences in clinical trials.<sup>46</sup> NORD applauds the inclusion of commitments to advance regulatory science in this area by, among other things, developing a framework for DHTs, establishing a cross-cutting committee tasked with implementing the framework, issuing guidances, holding public meetings, and ensuring that DHTs are considered in a consistent way across FDA.<sup>47</sup> As DHTs continue to advance, we are encouraged by their promise to be used to develop novel endpoints and commend FDA for committing to publish guidance to accomplish this goal. It will be essential that DHTs are validated and create quality, fit-for-purpose data that provide evidence of clinical benefit. NORD strongly believes that increasing the use and acceptance of digital tools and technologies can dramatically alter how clinical trials are conducted for rare diseases in the future. These advances should become permanent fixtures in drug development, and NORD applauds FDA for taking steps to do just that.

### Enhancing Regulatory Science and Tools to Support Drug Development and Review

Although not solely applicable to rare diseases, several commitments in the sections “Enhancing Regulatory Science and Expediting Drug Development” and “Enhancing Regulatory Decision Tools to Support Drug Development and Review” would improve drug development for rare

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<sup>42</sup> Guo, C., Ashrafian, H., Ghafur, S. et al. Challenges for the evaluation of digital health solutions—A call for innovative evidence generation approaches. *NPJ Digit. Med.* 3, 110 (2020). <https://doi.org/10.1038/s41746-020-00314-2>

<sup>43</sup> The Scientist. Pandemic Accelerates Trend Toward Remote Clinical Trials. (2021). Accessed 10/20/21. <https://www.the-scientist.com/careers/pandemic-accelerates-trend-toward-remote-clinical-trials-68679>

<sup>44</sup> McKinsey & Co. No place like home? Stepping up the decentralization of clinical trials. Accessed 9/18/21. <https://www.mckinsey.com/industries/life-sciences/our-insights/no-place-like-home-stepping-up-the-decentralization-of-clinical-trials>

<sup>45</sup> FDA. Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. (2021). Accessed 9/10/21. <https://www.fda.gov/media/136238/download>

<sup>46</sup> FDA. What is Digital Health? Accessed 10/20/21. <https://www.fda.gov/medical-devices/digital-health-center-excellence/what-digital-health>

<sup>47</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 65. (2021). Accessed 9/17/21. <https://www.fda.gov/media/151712/download>

disease and common disease patients alike. For example, the commitments around Model Informed Drug Development (MIDD), Complex Innovative Design (CID), new surrogate endpoints, and Drug Development Tools Qualification for Biomarkers are all methods to help sponsors utilize innovative methods to conduct clinical trials.

These advancements in regulatory science and drug development tools allow for more effective patient utilization, permitting sponsors to do more in clinical testing with fewer patients, which is important in rare diseases where populations are small. Commitments around MIDD and CID can help foster drug development advances to facilitate smaller trials with the same rigor, allow for more patients on treatment in the trial, and provide innovative ways to demonstrate the drug's benefit.<sup>48,49</sup> This is important for rare diseases which have small populations and may not be able to recruit enough patients for a control arm. Many rare diseases can be degenerative and rapidly progressing, so ensuring as many patients are on treatment as possible is optimal. The development of tools such as new surrogate endpoints allows sponsors to explore innovative ways to measure clinical benefit for a population when the natural history of the disease is not well known or the disease has slow progression, traits common in rare diseases.<sup>50</sup> Biomarker qualification is an important process that can provide certainty to sponsors when selecting a biomarker for a clinical trial within a specific context of use.<sup>51</sup> Biomarkers for rare diseases are important to target the underlying origin of a disease. Validating new biomarkers can help sponsors target those specific root causes of a rare disease.

NORD is also pleased with the proposal for Split Time Application Review (STAR) for efficacy supplements that address an unmet medical need.<sup>52</sup> The STAR program would split a supplemental efficacy application for an existing product into two parts for review to begin on the first part, while the second is finalized and submitted no more than 3 months later.<sup>53</sup> The goal of this program is to support faster review and approval of such a supplement.<sup>54</sup> Faster review of efficacy supplements for unmet need can benefit rare disease patients by facilitating speedier approval of new orphan indications for existing products.

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<sup>48</sup> FDA. CDER Conversation: Model Informed Drug Development. Accessed 10/20/21.

<https://www.fda.gov/drugs/news-events-human-drugs/cder-conversation-model-informed-drug-development>

<sup>49</sup> FDA. Complex Innovative Trial Design Pilot Meeting Program Frequently Asked Questions. Accessed 10/20/21.

<https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-pilot-meeting-program-frequently-asked-questions>

<sup>50</sup> FDA. Surrogate Endpoint Resources for Drug and Biologic Development. Accessed 10/1/21.

<https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development>

<sup>51</sup> FDA. About Biomarkers and Qualification. Accessed 10/11/21. <https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification>

<sup>52</sup> FDA. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. Page 14. (2021). Accessed 9/17/21. <https://www.fda.gov/media/151712/download>

<sup>53</sup> Pink Sheet. PDUFA VII Commitment Letter Outlines Real-Time Review Expansion, Hiring Goals. Accessed 10/20/21. <https://pink.pharmaintelligence.informa.com/PS144832/PDUFA-VII-Commitment-Letter-Outlines-RealTime-Review-Expansion-Hiring-Goals>

<sup>54</sup> Ibid.

## Areas for Further Consideration

While the Commitment Letter will undoubtedly help to advance drug development and review of rare disease therapies, NORD believes that the FDA can take some additional steps to further enhance the Commitment Letter.

### *PFDD*

In our July 2020 comments, NORD described the need for FDA to communicate back to patients the impact their data may have had on FDA's decisions about the application.<sup>55</sup> NORD believes that if there is value in patients taking the time to convey their experiences and preferences to FDA and sponsors in the context of the various patient-focused drug development meetings and listening sessions, then there should be a robust, consistent feedback mechanism to the patient community about what impact that input had on FDA's decisions. Consistent inclusion and use of the Patient Experience Data Table in review documents is a good start.<sup>56</sup> However, NORD encourages FDA to go further and provide descriptions of what data was helpful and why it was beneficial in the review process to allow external stakeholders to have a better understanding of what kinds of data are most impactful. We believe that developing a patient's understanding of how FDA utilizes their data will lead to more effective data collection and encourage patients to be more involved in the drug development process.

NORD also emphasized the importance of ensuring PFDD plans are discussed with FDA review divisions early in the drug review and approval process. Transparency as well as early, frequent interaction with FDA on how patients can contribute to a trial are vital to ensuring that patients are providing the maximum possible value in the drug development process. If sponsors continue to face difficulty getting these meetings,<sup>57</sup> NORD hopes that increased staffing will allow for more of these meetings at the earliest possible time.

### *Ensuring Appropriate Staffing for CDER Division of Rare Diseases and Medical Genetics*

NORD urges that PDUFA VII resources be allocated to CDER's Division of Rare Diseases and Medical Genetics (DRDMG) in a manner that reflects the increased workload that has resulted and will continue going forward in the next user fee cycle. The COVID-19 pandemic has resulted in dramatic staffing shortages across the Agency. While NORD supports embedding rare disease experts into all review divisions as envisioned in the Commitment Letter, it is

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<sup>55</sup> NORD. Docket No. FDA-2010-N-0128 for "Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments." (2020). <https://rarediseases.org/wp-content/uploads/2020/09/NORD-PDUFA-Comments.pdf>

<sup>56</sup> FDA. Assessment of the Use of Patient Experience Data in Regulatory Decision-Making. (2021). Accessed 10/20/21. <https://www.fda.gov/media/150405/download>

<sup>57</sup> Ibid.

important to recognize that the DRDMG can't fulfill this work, as well as its own review work, without adequate staffing.

### *Hiring and Retention*

Critical to fulfilling the goal of additional FTEs under PDUFA VII is a streamlined hiring process. Despite previous attempts to address the notorious hiring and retention challenges FDA faces, there continue to be concerns that the hiring process is unwieldy, and delays are frequent.<sup>58</sup> Although recent progress has been made,<sup>59</sup> this issue remains vitally important to maintain FDA operations. Staffing shortages can impact review times and result in delays in review and approval, which ultimately means patients wait longer to access treatment. But without adequate staffing, other critical work beyond product reviews, like training and engagement in regulatory science, suffers. NORD urges FDA to continue to work to address these challenges to the extent it is able and highlight the needs publicly so that external stakeholders can make appropriate efforts to help expedite the hiring process.

### Conclusion

NORD applauds industry and FDA for working together to develop a comprehensive Commitment Letter that will help to provide rare disease patients with access to therapies they need. We stand ready to remain a constructive partner to FDA throughout the PDUFA reauthorization process. For questions regarding NORD or the above comments, please contact Rachel Sher at [rsher@rarediseases.org](mailto:rsher@rarediseases.org).

Sincerely,



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National Organization for Rare Disorders



Edward Neilan, M.D., PhD  
Chief Medical and Scientific Officer  
National Organization for Rare Disorders

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<sup>58</sup> Booz Allen Hamilton. FDA Interim Hiring and Retention Assessment. (2020). Accessed 10/25/21. <https://www.fda.gov/media/138662/download>

<sup>59</sup> Pink Sheet. Top CDER officials discuss budget priorities, staffing and COVID. Accessed 10/21/21. <https://www.raps.org/news-and-articles/news-articles/2020/10/top-cder-officials-discuss-budget-priorities-staff>