



August 22, 2016

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2016-N-1895-0001: Prescription Drug User Fee Act; Public Meeting; Request for Comments

Dear Sir or Madam:

On behalf of the 30 million Americans with one of the nearly 7,000 known rare diseases, NORD thanks the Food and Drug Administration (FDA) for the opportunity to provide comments on the Agency's "Prescription Drug User Fee Act; Public Meeting; Request for Comments".

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

The reauthorization of the Prescription Drug User Fee Act (PDUFA) every five years gives the FDA, the regulated pharmaceutical industry, and patient stakeholders the opportunity to reexamine the drug and biologic review process to make drugs and biologics safer, more effective, and more patient-focused.

In 2012, the fifth PDUFA reauthorization included various regulatory and policy provisions that emphasized the importance of the patient in drug development and FDA review. For rare disease patients, the Food and Drug Administration Safety and Innovation Act (the authorizing legislation for PDUFA V) included the establishment of the Patient-Focused Drug Development (PFDD) Initiative, the strengthening of the Accelerated Approval expedited review pathway and the creation of the Breakthrough Therapy expedited review pathway, the requirement for FDA to maintain a list of outside experts in rare diseases, and the expansion of the benefit/risk efforts already underway.

The PDUFA VI Commitment Goals Letter outlined within this Request for Comments appears to build upon the successes of the PDUFA V agreement in many ways. Below are our comments on the specific sections of the Goals Letter followed by several additional policy areas to consider.

III. Proposed PDUFA VI Recommendations:

D. Enhancing Regulatory Science and Expediting Drug Development:

2. Breakthrough Therapies:

NORD supports the addition of resources to implement the breakthrough therapy program. As an added policy attached to the PDUFA V agreement, the breakthrough therapy program did not receive the required resources to ensure the FDA could appropriately implement the program. With over 400 breakthrough designation requests, it is clear the breakthrough program needs additional dedicated PDUFA user fees.

The breakthrough therapy pathway is particularly important for innovative orphan therapies. With breakthrough's "all hands on deck" approach, therapies that receive a breakthrough designation gain critical FDA attention and assistance in moving through the development and review process. However, with 46 breakthrough therapies approved by the FDA as of July 18, 2016, only five were for rare inherited disorders.¹

With the additional funds included in the Goals Letter, we hope the breakthrough therapy pathway can be opened to more orphan therapies for rare inherited disorders.

3. Early Consultation on New Surrogate Endpoints:

Biomarkers and surrogate endpoints represent some of the most promising innovative drug development tools. Rare diseases that had previously been thought of as unsolvable and untreatable could receive renewed attention with the advancement of the use of biomarkers or surrogate endpoints in clinical development.

Still, with so little known about the scientific underpinnings and disease progression in rare diseases, there is much progress still needed to be made in order to allow rare disease development to truly benefit from the use of biomarkers and surrogate endpoints. By discussing the use of surrogate endpoints earlier and more often, this provision could assist orphan drug developers in the use of surrogate endpoints in their study design.

We support the enactment of this provision, and hope to work with the FDA in ensuring these early consultations are available to orphan drug developers.

4. Rare Disease Drug Development:

NORD thanks the FDA and industry for their commitment to ensuring thorough yet expedient review of orphan therapies. This commitment is evident in the proposed expansion of the Rare Diseases Program (RDP) staff into the CDER teams reviewing orphan therapies, and the continued training of CBER staff on "flexible and feasible approaches to review".

We are very supportive of this provision for several reasons. First, we still hear too often from our patient organization members about FDA inappropriately requiring particular trial designs. For example, our member organizations have expressed strong concerns about participating in extra confirmatory

¹ Friends of Cancer Research. 2016. "Breakthrough Therapies. July 18, 2016. Accessed August 22, 2016. http://www.focr.org/breakthrough-therapies?title=&field_sponsor_value=&field_therapy_category_tid%5B%5D=45&field_fda_status_value%5B%5D=1

trials, being placed on a placebo control, or other forms of perceived inappropriate controls, and various other particularly arduous trial design requirements.

We also are aware of the wide spectrum of utilization of other flexible review techniques afforded by statute across review divisions for orphan drugs. Many review divisions are proficient in appropriately using expedited review pathways, accepting small trial sizes, using biomarkers or surrogate endpoints, or various other regulatory flexibility tools. Unfortunately, many other review divisions are not.

Finally, we continue to observe review divisions inappropriately deemphasizing quality-of-life improvements. Even if a therapy misses a primary endpoint, or perhaps a secondary endpoint, the quality-of-life improvements brought by that therapy still must be considered. Review divisions also have required particularly difficult endpoints to achieve, especially considering the small patient populations involved.

We believe each of these failures to appropriately use flexible regulatory review for orphan therapies arises from a fundamental misunderstanding of the rare disease patient experience. Rare disease patients are unique. They have a different risk/benefit formula than the general population. Their willingness to accept certain side effects is often misunderstood, and their prioritization of which symptoms to treat is unique. In addition, travel and participation in trials is often more difficult. We also believe that rare disease patients, particularly children, should not be required to go on a placebo and off of the therapy that is currently sustaining them.

All of these unique qualities need to be considered by review teams when reviewing orphan therapies. By placing RDP staff in each orphan drug review, these rare disease patient perspectives can be reflected and considered.

Any expansion of responsibility must be accompanied by a requisite expansion of resources and full-time employees (FTEs). The RDP already only has a handful of staff members, and to drastically expand their responsibilities as proposed in the Goals Letter without adding staff members would be irresponsible.

With added staff, we hope the FDA carefully considers how to assign RDP staff to particular reviews, and greater clarity on how FDA would do this is welcome. Given the broad spectrum of orphan therapies the FDA reviews each year, it may make sense to assign RDP staff to only one or a handful of review divisions rather than expecting them to participate in reviews across the disease spectrum. This would allow them to specialize in particular rare disease areas, and allow them to build an expertise in flexible review of therapies in certain disease areas.

This would also allow the RDP staff to proactively engage with the rare disease patient communities that may have therapies moving their way through the FDA review or pharmaceutical pipeline. While the collection of patient perspective data through the Patient-Focused Drug Development (PFDD) initiative and other avenues is ideal, the vast majority of rare disease patient organizations may be too small to undertake such a resource intensive endeavor.

We hope that RDP staff that specialize in certain disease areas can get to know the patients, their families and caregivers, and the organizations that represent them in order to have an understanding of

the disease experience, the patient's risk/benefit formula, and various other important considerations only the patient can provide. This task may include RDP staff traveling to family conferences, both in and outside of Washington, D.C., as well as various other opportunities to get to know the patients.

With these experiences and connections in hand, we believe the additional RDP staff are better equipped to facilitate the flexible review of orphan products.

5. Advancing Development of Drug-Device and Biologic-Device Combination Products Regulated by CBER and CDER:

NORD supports the investment of resources in the combination product review process, and is particularly supportive of the investment to the Office of Combination Products as well as each Center that plays a role in combination product review. With PDUFA's investment, we hope this provision will facilitate the review of both drug-led and device-led products, and does not lead to a situation in which drug-led products (PDUFA-led products) are afforded greater attention and resources compared to their device-led counterparts.

6. Enhancing Use of Real World Evidence for Use in Regulatory Decisionmaking:

We support the enactment of this provision, and thank the FDA and industry for their commitment towards advancing innovative opportunities to assess a therapy's safety and effectiveness. With the inherent difficulty of generating statistically significant conclusions from orphan drug clinical trials, the advancement of inclusion of real world evidence in regulatory decision making could greatly benefit the rare disease patient community.

8. Enhancing the Incorporation of the Patient's Voice in Drug Development and Decisionmaking:

One of NORD's primary regulatory priorities for many years has been the incorporation of the rare disease patient's perspective and experience into drug development and review. We were supportive of the creation of the PFDD initiative as part of PDUFA V, and have since supported the FDA in its efforts to expand PFDD opportunities to additional patient organizations through the creation of the externally-led PFDD meeting initiative and support for individual-disease guidance development.

We believe the proposals contained within the Goals Letter are a natural next step, and we are pleased to support their enactment. We hope these proposals will further encourage and facilitate orphan drug developers to include the patients and their perspective throughout the development of the therapy, and we hope to one day see each and every orphan drug that reaches the market reflect exactly what that specific patient population desires in a therapy.

To successfully reach this goal, we hope this provision will be implemented in the following ways. First, we strongly encourage the FDA to make any and all instructive guidances, public meetings, or other documentation to be accessible and digestible to the full spectrum of rare disease patient organizations. Only a handful of our 245 member patient organizations have the regulatory sophistication and dedicated resources to hold their own external PFDD meeting, conduct a scientific meeting with the FDA, or articulately participate in guidance development. We hope FDA considers the small individual

rare disease patient organizations and their limited capacities when putting forth materials to ensure all patients and their organizations can equitably participate.

Second, we hope the FDA will continue to encourage and support patient organizations in their conducting of externally-led PFDD meetings and creation of guidance for industry for their particular disease. We understand that we should move on from the over 20 FDA-led PFDD meetings, but we still believe the externally-led meetings and guidance development are great opportunities for our members. This being said, as already discussed, we also hope FDA will put forward additional opportunities for smaller organizations to participate who do not have the resources to conduct PFDD meetings or develop guidance for industry.

Finally, we understand some in the patient community are concerned with the timeline put forth for guidance development within this section. We certainly sympathize with the FDA's resources (or lack thereof), both financially and staff expertise-wise, to implement these sections. We hope this PDUFA agreement will result in the substantial increase in both the number of FTEs working on patient input as well as the expertise they bring.

We hope that if the FDA implements this section using the timelines proposed, that the FDA will advise organizations such as NORD and others who are actively working on the science of patient input on how and where to make progress in the meantime.

9. Enhancing Benefit-Risk Assessment in Regulatory Decisionmaking:

NORD supports the continuation and expansion of FDA's "enhanced structured approach to benefit-risk assessment". Rare disease patients' benefit-risk formulas are the likeliest to be misunderstood or misconstrued due to their small, dispersed, and heterogeneous patient populations. By investing in FDA's structured benefit-risk assessment development, the FDA and industry are committing to the better and more representative inclusion of rare disease patients' benefit-risk assessment. We support the enactment of this provision.

10. Advancing Model-Informed Drug Development, and 11. Enhancing Capacity to Review Complex Innovative Designs:

We are supportive of both of these provisions as orphan therapies often require innovative and complex trial designs in order to show safety and effectiveness. For these reasons, the advancement of model-informed drug development could open the door for rare disease therapeutic development that may not have moved forward otherwise.

Industry's commitment to enhancing the FDA's capabilities in reviewing complex innovative designs is important in ensuring this occurs, and we are thankful to industry and FDA for prioritizing this burgeoning area.

13. Enhancing Drug Development Tools Qualification Pathway for Biomarkers:

The strengthening of FDA's biomarker qualification process is an important priority for NORD. As already discussed, we view the use of biomarkers and surrogate endpoints as impactful drug

development tools that could greatly spur development in rare diseases that are difficult to develop in. The public meeting, guidance development, and website creation will all facilitate the process for biomarker qualification, and hopefully eventually lead to the use of biomarkers in orphan drug development.

G. Improving FDA Hiring and Retention of Review Staff

As a founding member of the Alliance for a Stronger FDA, no one is more supportive than NORD in ensuring FDA is adequately funded, and is able to hire and retain high quality candidates. Special expertise is needed to appropriately review orphan therapies, and it is important to NORD and rare disease patients that the FDA has the capabilities in house to appropriately review orphan therapies.

Additional Areas to Consider:

As the PDUFA agreement progresses towards final enactment, NORD would like to propose additional areas to consider policy changes.

Office of Orphan Products Development:

First, NORD has been made aware of an increase in the number of orphan designation requests being made to the Office of Orphan Products Development (OOPD). It is our understanding that because of this increase in designation requests, and without the subsequent increase in staff capabilities or resourcing, the OOPD has had to extend its internal review goal from a 90 day review to a 120 day review.²

We find this additional delay troubling, and we request that OOPD is given the required resources to complete orphan designation determinations within the 90 day window. We understand that much of the funding for OOPD is provided by the user fees provided to the Office of the Commissioner. We hope the disbursement and distribution of such funding to the OOPD is reflective of the growing responsibilities they have incurred.

Office of Patient Affairs:

While NORD is certainly supportive of the growing number of opportunities for patients to participate within FDA processes, we are growing concerned about the lack of coordination amongst such opportunities and are worried patients may be confused on how best to participate.

For this reason, we have proposed that the current Patient Liaison Program (PLP) housed within the Office of Health and Constituent Affairs be elevated to become the Office of Patient Affairs directly beneath the Commissioner (the same level as the Office of Women's Health and Office of Minority Health).

This location will allow the Office of Patient Affairs to more visibly publicize patient involvement opportunities, and assist in the coordination of CDER's PFDD initiative and Professional Affairs and

² Gayatri Rao, 2016. "The Rise in Orphan Drug Designations: Meeting the Growing Demand". FDA Voice. July 18, 2016. Accessed August 22, 2016. <http://blogs.fda.gov/fdavoices/index.php/tag/fdas-office-of-orphan-products-development-oopd/>

Stakeholder Engagement (PASE) office, CBER's patient involvement opportunities, CDRH's efforts on patient perspective data and the Patient Engagement Advisory Committee, and the various opportunities the PLP already oversees, among others.

This office will be better equipped to handle patient inquiries on expanded access and can better assess patient's conflict-of-interest determinations. All in all, we believe this office could greatly improve rare and common disease patient's involvement with the FDA, and we are hopeful for its enactment. For more information on this, please read our [full proposal](#) and [one pager](#).

We thank FDA for the opportunity to comment, and we look forward to working with FDA to ensure the continued growth in therapeutic development for rare diseases, and the continued involvement of patients in the development and review process. For questions regarding NORD or the above comments, please contact me at mrinker@rarediseases.org or (202) 588-5700, ext. 102.

Thank you in advance for your consideration.

Sincerely,

A handwritten signature in blue ink, appearing to read "Martha Rinker". The signature is fluid and cursive, written over a light blue rectangular background.

Martha Rinker, J.D.
Vice President, Public Policy