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NORD Comments on the PDUFA Commitment Letter and Federal Register Notice [Docket No. FDA-2026-N-8163]

Priorities for rare disease drug development, regulatory science, and an effective FDA

The National Organization for Rare Disorders (NORD), on behalf of the one in ten Americans living with a rare disease, appreciates the opportunity to comment on the Prescription Drug User Fee Act (PDUFA) commitment letter and related Federal Register Notice. For more than 40 years, NORD has served as a leading patient advocacy organization for people affected by rare diseases—conditions that, under the Orphan Drug Act, affect 200,000 or fewer people in the United States—and for the organizations that represent them.

Together with more than 350 patient organization members, NORD works to improve the health and well-being of people with rare diseases by advancing care, research, and public policy. Every person with a rare disease should have timely access to high-quality, affordable health care and therapies that reflect their individual medical needs and informed preferences.

NORD's comments are guided by four priorities:

- Advancing the Rare Disease Innovation Hub
- Strengthening the Patient Voice in Drug Development and Regulatory Decision-Making
- Supporting Innovation for Rare Diseases
- Ensuring a Well-Resourced and Agile FDA of the Future

NORD offers the following recommendations to strengthen the final PDUFA framework. We support timely reauthorization while emphasizing that speed must be

paired with scientific rigor, meaningful patient engagement, transparency, and sufficient resources to sustain a capable and responsive FDA.

Comments

Advancing the Rare Disease Innovation Hub

RISE Workshops

NORD supports continued RISE workshops as a forum for addressing cross-cutting scientific and regulatory challenges in rare disease development. Workshops should include diverse disease communities, academic experts, clinicians, sponsors of different sizes, and representatives from relevant FDA centers. Agendas and selection criteria should be transparent, materials should be publicly available, and each workshop should produce concrete outputs—such as methodological recommendations, research priorities, or follow-up actions—with timelines and accountable owners.

NORD welcomes commitments to hold ten RISE meetings, publish case studies showing how patient experience data informed review, and convene a public meeting on those case studies. These activities can promote shared learning across the rare disease ecosystem and improve the development and use of novel endpoints, biomarkers, natural history data, external controls, and other fit-for-purpose tools. FDA should publish clear eligibility criteria, lessons learned, and practical examples; ensure that small sponsors and under-resourced patient organizations can participate; and establish a mechanism for translating successful approaches into review practice and future guidance. NORD appreciates the opportunity to engage with the Rare Disease Innovation Hub and supports its mission to encourage meaningful coordination across centers and offices on rare disease issues.

Strengthening the Patient Voice in Drug Development and Regulatory Decision-Making

Communication and Stakeholder Engagement

Predictable, timely communication between FDA and sponsors—including pre-submission meetings, mid-cycle communications, and other milestone meetings—can identify issues early and improve the efficiency of product development and review. We appreciate that the commitment letter establishes clear expectations for meeting requests, briefing materials, written responses, follow-up items, and escalation pathways, while promoting consistency across review divisions.

Current formal communication pathways, however, provide limited opportunities for patients, caregivers, rare-disease-treating clinicians and researchers to contribute relevant evidence. FDA should create appropriately managed avenues for qualified expert input when it can inform regulatory decision-making such as endpoint selection, clinical meaningfulness, trial feasibility, benefit-risk assessment, or postmarket needs. Such engagement should supplement—not compromise—the integrity of sponsor communications or confidential review processes. FDA should also explain how external input is evaluated and incorporated into decisions.

Benefit-Risk Assessment

NORD supports continued use and enhancement of FDA’s structured benefit-risk framework. Assessments should explicitly identify the evidence and uncertainties considered, the available treatment landscape, disease severity, unmet need, treatment burden, and the preferences of patients and caregivers. FDA should continue to explain how patient input affected key judgments and should revisit benefit-risk conclusions when important postmarket evidence emerges.

Patient-Focused Drug Development and Patient Experience Data

Patient experience data should inform development from the earliest stages, including endpoint selection, acceptable trial burden, and interpretation of clinically meaningful benefit. NORD supports publication of case studies, public meetings, and staff training, but these activities should be designed to produce consistent practice across review divisions. FDA should clarify evidentiary expectations, provide feedback early, and publish examples showing both successful uses of patient experience data and common limitations.

FDA should also reduce participation barriers for small and historically underrepresented communities by offering technical assistance, accessible meeting formats, and plain-language materials. Engagement should reflect the diversity of each disease community, including variation in age, geography, disability, disease stage, socioeconomic status, and access to care.

Supporting Innovation for Rare Diseases

Postmarket Safety and the Sentinel System

NORD appreciates continued support for the Sentinel active postmarket surveillance system. The 2024 assessment found that Sentinel contributed to FDA’s public health mission, and continued investment can strengthen the Agency’s ability to identify, evaluate, and communicate safety signals. FDA should provide accessible reporting on

how Sentinel analyses are initiated, how findings influence regulatory actions, and how the system analyzes rare diseases and small patient populations.

Rare Disease Drug Development

NORD welcomes the commitment letter's focus on rare disease drug development. Integrating rare disease program staff from CDER and CBER into review teams can improve consideration of small populations, heterogeneous disease presentation, limited natural history information, and novel trial designs. No single agency can maintain in-house expertise in every rare disease, however. Review teams should systematically seek external expertise from patients, caregivers, treating clinicians, researchers, and disease-specific organizations, with safeguards for confidential commercial information, personal privacy information as well as conflicts of interest. FDA should provide a clear explanation of how that expertise informed the review. Lastly, we request additional information regarding the methodology behind assigning individual rare disease program staff into review teams.

The commitment letter repeatedly refers to regulatory "flexibility." NORD encourages FDA to describe this concept as rigorous, context-sensitive application of statutory and scientific standards rather than as a lesser evidentiary standard. Approaches should be fit-for-purpose and may include innovative statistical methods, Bayesian models, natural history controls, validated biomarkers, real-world evidence, and adaptive or decentralized trial features where appropriate. Benefit-risk judgments should meaningfully incorporate the perspectives of people living with the disease, who may weigh uncertainty, treatment burden, and risk differently from regulators or sponsors.

FDA should promote consistency by documenting precedents, publishing anonymized case studies, and training review staff on rare disease methods. When an approach is not accepted, the Agency should provide a clear scientific rationale and identify feasible alternatives early enough for sponsors and patient communities to respond.

Real-World Data and Real-World Evidence

NORD supports continued development and appropriate use of real-world data and real-world evidence. For rare diseases, registries, electronic health records, natural history studies, claims, digital health technologies, and patient-generated data may supplement limited trial evidence, support external controls, characterize disease progression, and strengthen postmarket surveillance. FDA should update guidance as methods evolve, clarify fitness-for-use standards, and encourage early consultation on data quality, missingness, bias, interoperability, and statistical analysis.

To maximize value, FDA should promote common data elements, sustainable registry governance, and approaches that allow responsible data linkage while protecting privacy and security of all relevant information. Lessons from successful and unsuccessful submissions should be shared in a manner that protects confidential information - both patient and commercial - and helps the field converge on reliable practices.

Cell and Gene Therapies

NORD supports maintaining sufficient CBER expertise and resources for cell and gene therapy products. Stable staffing and leadership is essential because these programs present complex issues involving manufacturing, comparability, durability of response, long-term follow-up, and potentially small or single-arm clinical studies. FDA should preserve institutional knowledge, expand specialized training, and ensure that staffing keeps pace with the scientific and review workload rather than relying solely on existing resources.

FDA should continue outreach to patients, caregivers, clinicians, researchers, manufacturers, and other stakeholders as it refines approaches to evidence generation and the evaluation of safety and effectiveness. Guidance should address fit-for-purpose endpoints, use of external controls and real-world evidence, manufacturing changes, long-term monitoring, and communication of uncertainty. For rare conditions, the Agency should provide early, coordinated advice that reduces avoidable development delays while maintaining rigorous standards.

Type C meetings for Endpoints

The Rare Disease Endpoint Advancement pilot currently centers on sponsor participation, yet patient organizations, academic researchers, and public-private consortia also develop symptom scales, clinical outcome assessments, biomarkers, and digital measures. When an endpoint is supported by sufficient evidence, the Agency should facilitate its reuse across development programs and communicate the evidentiary basis for acceptance. Shared endpoints can reduce duplication, conserve scarce patient populations, and accelerate development across an entire disease area.

Ensuring a Well-Resourced and Agile FDA of the Future

Assessment of the Review Program

NORD supports an independent, third-party assessment of the review program and efforts to improve operational efficiency. The assessment should evaluate not only whether FDA meets review timelines, but also whether reviews are appropriately resourced, and responsive to the needs of patients. Measures should address the

integration of patient experience data and the use of external expertise. Findings should be accompanied by an implementation plan and regular progress reporting.

Resource Management and Workforce Stability

FDA's public health mission depends on an experienced, multidisciplinary workforce. Although the proposed financial structure is intended to restore staffing to 2025 levels, headcount alone is not an adequate measure of capacity. The Agency needs well-trained reviewers, statisticians, clinicians, project managers, regulatory scientists, information-technology professionals, and administrative support staff, as well as sufficient resources for retention, onboarding, succession planning, and continuing education. Congress and FDA should protect workforce stability and minimize disruptive hiring cycles.

Conclusion

NORD urges FDA and Congress to finalize a PDUFA framework that pairs timely review with scientific quality, meaningful patient engagement, transparent decision-making, and a stable expert workforce. The rare disease community stands ready to collaborate on implementation, evaluation, and continuous improvement so that regulatory policy better supports safe, effective, and urgently needed therapies.

For questions regarding NORD or the above comments, please contact me at ctenenbaum@rarediseases.org

Sincerely,

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