Patrizia Cavazzoni, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10001 New Hampshire Ave
Silver Spring, MD 20903

March 17, 2023
Re: Docket No. FDA-2022-N-3226 for "Opportunity for Feedback on Development and Dissemination of Educational Materials on Rare Disease Drug Development"

Dear Dr. Cavazzoni,

On behalf of the more than 25 million Americans living with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance for industry, FDA staff, and other stakeholders titled "Opportunity for Feedback on Development and Dissemination of Educational Materials on Rare Disease Drug Development."

NORD is a unique federation of non-profits and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in policy, research, and care. NORD was founded 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing this landmark law. Since that time, patient education on rare disease drug development has been a central part of our mission. For instance, NORD is currently creating a patient- and caregiver-focused educational series on advanced topics in rare disease drug development through an FDA grant. NORD also serves as the leading institution dedicated to educating lawmakers and government bodies on the patient's experience of living with a rare disease. Because drug development can be extremely challenging for rare diseases, NORD supports patients by creating patient registries, holding educational workshops, supporting patient-focused drug development (PFDD), and providing grants to researchers. Finally, NORD's 31 Rare Disease Centers of Excellence link the nation's most eminent rare disease researchers and clinicians.

NORD strongly supports CDER's ARC program and specifically the "Learning and Education to Advance and Empower Rare Disease Drug Developers" (LEADER 3D) educational series. Closing key educational gaps will help bring life-saving therapies to the rare disease community more quickly. NORD is pleased to provide the specific comments and recommendations below, informed by 40 years of experience working constructively with our rare disease community including patients and caregivers, researchers and clinicians, pharmaceutical and biotechnology companies, as well as FDA and NIH, to help bring more rare disease therapies to more patients.

Recommendation 1: Rare disease drug development stakeholders have unique and diverse backgrounds and educational needs; intentionally create educational materials that meet these stakeholders where they are.

In the rare disease space, patient advocacy groups, academic researchers, and small biotech start-ups often play key roles in research and data collection. Educational materials must be suited for and accessible to

these diverse audiences. To effectively empower these diverse stakeholder groups to engage in drug development through education, NORD recommends the following approaches:

a. **Many stakeholders need educational content to build a foundation that bridges to the advanced content specific to challenges of rare disease drug development.** Albeit diverse and heterogenous in background, many of the rare disease drug development stakeholder groups share many of the same knowledge gaps, including limited regulatory and legislative experience, as well as limited access to specialized expertise ranging from statistics and epidemiology to pharmacology and clinical sciences that is more readily accessible for larger pharmaceutical companies. We urge FDA to integrate some foundational education to bridge this knowledge gap. Without adequately addressing these foundational knowledge gaps, success of the more specialized educational objectives will likely remain limited.

b. **Make educational materials easily accessible to an adult learner audience, including individuals with disabilities or unique access challenges.** Many rare disease drug development stakeholders wear multiple hats. As a case in point, according to NORD's recent survey of Patient Advocacy Groups, among respondents, 60% of the organizations were started by a parent of a child with the disease, often with little or no background in research and medical affairs while only 20% of patient advocacy groups were founded by medical professionals. Given the diversity of stakeholders in the rare disease drug development space, tailor educational materials to an educated lay audience. For instance, ensure you explain and define key terminology and adapt the reading level to all key audiences. NORD also recommends including closed captioning and screen reading audio for those that are visually and hearing impaired, as well as other accommodations for those with other conditions or social determinants of health impacting the ability to access these modules including language and broadband challenges. Finally, as a best practice, to ensure educational materials for adult learners are engaging and instructional, we recommend being intentional about the length and complexity of individual educational materials, the use of animation and other media formats, and the selection of stories and individuals to highlight to ensure broad representation so that educational materials resonate with the maximum number of stakeholders.

c. **Partner with trusted voices and be intentional in how you present and where and how you post the educational materials.** The best educational materials are useless if the intended audience cannot find them. A variety of educational materials on topics relevant to rare disease drug development, from clinical trials to real-world evidence and beyond, already exist but in the absence of a centralized and trusted hub, can be hard to find and access, limiting their impact.
    i. By having this educational series in a centralized location and disseminated through a prominently displayed and easy to find website, FDA can help ensure easy access by the intended audience. We encourage this information to be easily accessible on the front pages of the ARC page, so all pertinent stakeholders are aware of these educational materials.
    ii. Presentation of the content will be key to success; the complex subject matter should be broken down into digestible, succinct pieces where users can easily understand the materials with limited time. Intentional presentation of the different educational resources in a cohesive and logical way helps guide the learner through the content and aids with learning and retention.

iii. When the content becomes available, a campaign of outreach to the target audience (through webinars, social media, or other means) would help promote awareness and ensure the education reaches the intended targets.

d. **Assess, evaluate, and refine your educational materials to ensure they meet, and continue to meet, the community's need.** NORD also strongly encourages the FDA to implement a feedback loop so learners can easily suggest improvements to the module.

Recommendation 2: Create a comprehensive curriculum that spans the complete drug development process and goes beyond the scientific and regulatory dimensions of drug development outlined in the FDA feedback document.

Successfully developing a drug to come to market, for a rare disease, requires many different disciplines and can break down at many stages. While the three topics suggested in the FDA feedback document are important to the patient population, once a basic understanding of drug development is established, these educational materials should discuss all key concepts important specifically to rare disease drug development.

a. Guidance and best practices for engagement with drug sponsors, FDA, and other key stakeholders are key to rare disease drug development, but educational materials to address this issue to date remained scarce. This type of educational content consistently ranks high among key gaps identified by our patient and the small biotech industry. In fact, in NORD's recent membership survey, patient advocacy groups were asked to describe their relationship with industry, their participation in research, and how they disseminate medical information. For all three of these categories, 151 patient advocacy groups completed the survey and over 55% of patient advocacy groups stated they struggled in these areas. Similarly, 21% of queried organizations want a guide for how to request a meeting with FDA and 23% want guidance on how to prepare for a meeting with FDA. Other areas scoring high on the priority list include a guide for what Orphan Drug Designations are and how to request them, as well as more information about Advisory Committee meetings and how to participate.

These findings mirror what we consistently hear from pharma and biotech start-up companies, as well as providers including our NORD Rare Disease Centers of Excellence. The need for better tools and more guidance on how to work together effectively on the development of rare disease drugs is universal and largely unmet. Specifically, NORD recommends covering at least the following topics in the educational materials:

i. The role of patient advocacy groups in rare disease drug development and best practices for engagement and collaboration between sponsors and patient advocates
ii. Early engagement with FDA on a rare disease drug development program, potentially before an Investigational New Drug (IND) application is filed
iii. Best practices for engagement before, during, and after submission of a New Drug Application (NDA)
iv. How to engage with FDA and drug sponsors to consider repurposing a drug

b. Ensure educational content specifically addresses the unique challenges of rare disease drug development and provides practical tools and tangible solutions. The development of rare disease drugs comes with its own unique challenges, often including the lack of natural history data, small, geographically dispersed and heterogenous populations, and complex disease

pathology.[1] As a result, in many areas of drug development, ranging from epidemiology and trial design to dose optimization, endpoint selection and validation, standard best practices are not feasible without modifications and adaptations. Yet, educational materials specific to the adaptation of these foundational concepts to rare disease drug development is often missing. Specifically, NORD recommends including at least the following topics in the educational material:

i. The unique challenges associated with rare disease drug development and strategies and the best practices for overcoming them (e.g., patient recruitment and retention, sample size, inclusion and exclusion criteria, dose finding and endpoint validation)
ii. Clinical trial designs specific to rare diseases
iii. Collection and use of Natural History Studies and Real-World Evidence/Real World Data in rare disease drug development
iv. Developing and validating clinical endpoints including Clinical Outcome Assessments for rare disease populations
v. Collection and use of robust, high quality Patient Experience data

c. **The development of New Molecular Entities only constitutes a small fragment of the drug development ecosystem for rare diseases, even though much of the education tends to focus on this topic.** Off-label use, drug repurposing, and compassionate use are common in the rare disease space and are vital components of rare disease drug development, albeit not well understood by many key stakeholders. For this reason, NORD recommends addressing educational gaps on key topics including:

i. An introduction to Orphan Drug Law and Regulations
ii. Drug repurposing and off-label use
iii. Programs and pilots to help spur rare disease drug development

Recommendation 3: Continue to engage the rare disease drug development community and leverage the power of stories and personal connections.

a. **Consider integrating in-person or remote education and train-the-trainer models as part of the educational strategy to build an engaged community and better understand remaining educational gaps.** NORD has been providing in-person and online education about research and drug development for patients, caregivers, and patient organizations since the 1980s at its patient conferences. For example, at NORD's Rare Diseases and Orphan Products Summit each year, NORD fosters collaboration with the FDA to promote a better understanding of drug development and how the various stakeholders can get involved. At NORD's Breakthrough Summits, patient advocates and caregivers engage in fireside chats with center directors, breakout sessions, and listen to FDA plenary panels. In addition to in-person events, webinars have also been tremendously useful in building community; for instance, in July 2022, NORD hosted a webinar on "Rare Disease Drug Development: A Community Conversation," which attracted more than 600 registrants across the rare disease community, including many from patient organizations. In holding these meeting sessions with patient advocates,

[1]FDA. (2022, December 31). Rare diseases at FDA. U.S. Food and Drug Administration. Retrieved March 9, 2023, from https://www.fda.gov/patients/rare-diseases-fda#:~:text=Drug%2C%20biologic%2C%20and%20device%20development,make%20conducting%20clinical%20trials%20difficult.

we can hear first-hand about the current educational gaps and issues surrounding the patient's experience in rare disease drug development.

b. **Leverage the power of storytelling.** In the past 40 years, we have seen tremendous progress in rare disease research and drug development, including new opportunities for patients to participate in research and in the number of ways patients are getting involved.[2] Leveraging these stories as case studies provides unique opportunities to engage learners in the educational content. To provide just one illustrative example, just last month, on Rare Disease Day, the FDA approved the first treatment for Friedreich's Ataxia, a rare neuromuscular disease that develops rapidly over a brief period of time. The new therapy, developed through clinical trials and an open-label extension study, [3] like so many others in our rare disease space, is in large part a result of patient advocacy and education on the processes and guidelines for drug development. The patient advocacy community was pivotal in providing patients with educational materials on how clinical trials work, the treatment pipelines, and its history of drug developments, which garnered a patient population large enough to enable this development.[4] The successes we have seen in patient groups educating and mobilizing the community and taking a central role in the development process emphasize the need to take a comprehensive approach, both regarding the stakeholders to engage and the educational content to provide.

Greater patient involvement in the drug development process and incorporation of the patient voice at all stages of development is one of NORD's main priorities. We thank the Agency again for the opportunity to comment and look forward to working with FDA to ensure rare disease patients and patient advocacy organizations can fully participate within this important effort.

Sincerely,

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[2] Barriers to Rare Disease Diagnosis, Care, and Treatment in the U.S.: A 30-Year Comparative Analysis. National Organization for Rare Disorders. (2020, November 19). Retrieved March 9, 2023, from https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf

[3] First Medication to Treat Friedreich's Ataxia Approved on Rare Disease Day. Friedreich's Ataxia Research Alliance. (2023, February 28). Retrieved March 9, 2023, from https://www.curefa.org/news-press-releases/first-medication-to-treat-friedreich-s-ataxia-approved-on-rare-disease-day

[4] Reata Pharmaceuticals announces FDA approval of SKYCLARYS™ (omavaloxolone), the first and only drug indicated for patients with Friedreich's ataxia. Reata Pharmaceuticals Inc. (2023). Retrieved March 9, 2023, from https://www.reatapharma.com/investors/news/news-details/2023/Reata-Pharmaceuticals-Announces-FDA-Approval-of-SKYCLARYS-Omaveloxolone-the-First-and-Only-Drug-Indicated-for-Patients-with-Friedreichs-Ataxia/