LEADER 3D: Learning and Education to Advance and Empower Rare Disease Drug Developers

PUBLIC REPORT OF EXTERNAL STAKEHOLDER ANALYSIS

FDA | **U.S. FOOD & DRUG ADMINISTRATION**

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

Tables

Figures

I. EXECUTIVE SUMMARY

In support of efforts to encourage innovation and mitigate challenges associated with rare disease drug development, the U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) worked with an independent third-party contractor, to conduct interviews with rare disease drug development community stakeholders and performed a review of public docket comments to identify educational opportunities across topics in rare disease drug development. This report summarizes the findings from the analysis of these interactions and provides recommendations to continue efforts for expanded outreach and education to rare disease drug development stakeholders.

A. Summary of Findings by Topic Area

A summary of the assessment findings for each of the identified topics is described below.

1. Nonclinical

For the nonclinical topic, participants pointed to challenges with animal models. Interviewees indicated they have limited access to information on appropriate alternative models for rare diseases that do not have suitable animal models. They also shared that they usually rely on academic researchers to develop animal models, and since animal models are generally developed prior to clinical studies, there is sometimes a disconnect between the nonclinical program and clinical program on regulatory expectations for the development of an animal model or alternative animal models. The Rare Disease Drug Development (RDDD) community also mentioned they lack a clear understanding of how much data are needed to assess whether a therapy is a strong candidate to move forward from a nonclinical program to a clinical program.

2. Dose-Finding

For the topic of dose-finding, the RDDD community acknowledged the difficulty in selecting the optimal dose that balances efficacy and adverse events for rare disease clinical trials, particularly in instances where the patient populations are small and heterogeneous. The example of pediatric populations was cited by the RDDD community. Several participants suggested that FDA-led workshops be held, and guidance documents published to elucidate best practices to characterize the dose-exposure-response relationship, especially when limited data are available. The RDDD community also recommended that FDA develop educational materials explaining how sponsors may extrapolate clinical data from adult populations to pediatric populations.

3. Natural History Studies and Registries

For the topic on natural history studies and registries, the RDDD community acknowledged the valuable insights gained from natural history studies but noted the need for data sharing through conferences and scientific papers, especially when the patient population is small and there is a high unmet need to develop drugs. Industry participants indicated that they obtain natural history and registry data through outreach and partnership with PAGs and observed that these studies are usually led by members of academia. Industry participants also voiced challenges with the perceived lack of regulatory rigor within natural history data while noting that academics who are associated with these types of studies may be less familiar with regulatory standards and expectations. Industry conveyed a desire for further guidance on the use of natural history and registry data and requested specific case studies explaining when and how natural history data could be appropriately incorporated into a clinical study as an external control group. The RDDD

community suggested FDA consider providing additional guidance to sponsors on regulatory expectations for collecting and incorporating fit-for-purpose Real-World Data (RWD) to support Real-World Evidence (RWE) in clinical studies for rare disease drug development.

4. Novel Endpoint and Biomarker Development

When developing a drug for a rare condition where drug development has not previously occurred, the RDDD community expressed that the lack of precedent for endpoint selection and the potential need to develop novel biomarkers and endpoints adds additional risk and challenge. They discussed difficulties in developing robust statistical approaches for analyzing novel endpoints in RDDD due to small study populations.

Those interviewed requested more information on FDA's expectations for measuring clinically meaningful changes in trial endpoints. They requested more information on the role biomarkers may play when establishing evidence of clinical efficacy, and they requested information on the type and amount of data that should be collected for different novel trial endpoint types, such as composite, multicomponent, intermediate, and surrogate endpoints when the endpoints will be used to support a marketing application.

The interviewees noted that additional engagement and input from FDA focused on biomarker development; developing Clinical Outcome Assessments (COAs); validation of endpoints; and composite and multi-component endpoint development could help sponsors understand regulatory requirements for novel endpoint development associated with rare diseases.

5. Clinical Trial Design and Analysis

For the topic of clinical trial design and analysis, the RDDD community shared a common concern regarding patient recruitment. They noted that, apart from challenges with small patient populations, a major challenge in recruiting participants is patients' reluctance to participate in a clinical trial without the opportunity of receiving an investigational product (i.e., the risk of a participant being randomized into the placebo group). In addition, stakeholders identified disease diagnosis and patient stratification as primary challenges in patient recruitment. During the interviews, stakeholders expressed a desire for additional information (e.g., case scenarios and examples) on clinical trial design, with special focus on the challenges associated with RDDD, including conducting trials with small patient populations. They also requested guidance on statistical approaches for small patient populations and model-informed drug development to overcome common limitations (e.g., small patient sample size, general lack of natural history data, and ability to run only a limited number of trials) encountered in RDDD.

6. Rare Disease Drug Development Regulatory Considerations

For RDDD regulatory considerations, a challenge with rare disorders is that each disease is unique and while the RDDD community acknowledged that disease-specific guidance documents may not be feasible, they opined that rare disease drug development necessitates additional discussions with the Agency. Specifically, stakeholders requested that there be more meetings with the Agency to address complex questions unique to RDDD and most stakeholders expressed a desire for more direct engagement with FDA to receive regulatory support. Stakeholders stated that more opportunities for open dialogue and interaction with FDA would be beneficial and cost-effective to clinical programs, allowing them to more efficiently align their research programs with regulatory expectations. They were also interested in receiving additional information from FDA on considerations regarding the use of expedited programs for rare disease products. In addition, PAGs observed that academic stakeholders interested in RDDD demonstrate limited familiarity with FDA guidance documents on RDDD topics. Guidance documents are not published in

PubMed, which is a prominent informational resource used by academic and clinical colleagues. PAGs also reiterated their stakeholders' (i.e., patients and families, researchers, and advisory committees) have limited understanding of the regulatory process and this can be a barrier in championing the development of rare disease drugs.

II. INTRODUCTION

Rare disease drug development can be challenging for numerous reasons, such as small and sometimes very small patient populations, genotypic/phenotypic heterogeneity within a disease, and novel endpoint development and selection, all in the context of often serious and life-threatening diseases without adequate approved therapies. These commonly faced rare disease drug development challenges can make study design, conduct, and interpretation complex.

The Agency, through its sixth reauthorization of the Prescription Drug User Fee Act (i.e., PDUFA VII), continues to commit resources to enhancing regulatory science and advancing development of drugs for rare diseases. Through FDA's PDUFA VII commitments[1], the Center for Drug Evaluation and Research (CDER) Rare Diseases Team (RDT), at the U.S. Food and Drug Administration (FDA) aims to facilitate, support, and accelerate the development of drug and biologic products for the benefit of patients with rare disorders. CDER recognizes the unique challenges drug developers face in demonstrating the safety and effectiveness of drugs that treat rare diseases. In May 2022, CDER was proud to launch the Accelerating Rare disease Cures (ARC) Program to bridge the gap between the complexities of rare disease drug development and the pressing need to have treatment options for patients with rare diseases. As part of the ARC program, CDER's RDT inaugurated the Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) initiative to better understand and address the unique challenges in bringing rare disease products regulated by FDA CDER to the market.

To support this effort, FDA CDER engaged an independent contractor, Booz Allen Hamilton, to collaborate with RDT (i.e., the project team) and complete an in-depth assessment and draft this public report. This report identifies educational gaps and needs to help inform the development and dissemination of educational materials specific to Rare Disease Drug Development (RDDD). The in-depth assessment completed by the project team included (1) reviewing existing RDDD educational materials, (2) conducting focus groups[2] and stakeholder interviews, and (3) analyzing public docket comments to understand the perceived challenges and identify topics that would benefit from the expansion or development of educational materials and topics that require an increased awareness of FDA resources already in existence.

The stakeholder interviews included members of industry (e.g., small-to-medium sized and large pharmaceutical companies, contract research organizations, and professional trade organizations), PAGs, and academia (including academics and clinicians) engaged in rare disease clinical research. This report identifies stakeholder perceptions regarding RDDD challenges obtained from interviews and comments provided in a public FDA docket.[3] The insights gathered are presented in this report and are divided into six relevant topics of interest (1) nonclinical, (2) dose-finding, (3) natural history studies and registries, (4) novel endpoints and biomarker development, (5) clinical trial design and analysis, and (6) RDDD regulatory considerations. This information will inform FDA CDER's shorter- and longer-term development of educational materials and subsequent efforts to disseminate curricula to relevant stakeholders.

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[1] https://www.fda.gov/media/151712/download
[2] Focus groups comprising U.S. Government (USG) employees affiliated with non-FDA USG agencies
[3] Docket (FDA-2022-N-3226)

III. ASSESSMENT METHODOLOGY

This section describes the external stakeholder assessment and the approach for engagement, data collection, synthesis, and analysis. For this assessment, external stakeholders (RDDD community) encompassed the pharmaceutical industry (i.e., small-to-medium, and large-sized pharmaceutical companies, contract research organizations, and professional trade organizations), PAGs, and academia (including academics and clinicians).

A.   Overview of Our Five-Step Approach

The project team gathered comprehensive data on the current landscape of rare disease educational materials by engaging the RDDD community through interviews and a public docket posted on regulations.gov.[4] The project team's approach consisted of five steps: (1) identify external stakeholders and develop outreach communications, (2) develop interview guides and docket language, (3) create a data collection instrument (DCI), (4) collect and analyze data, and (5) generate findings and recommendations.

Identify External Stakeholders and Develop Outreach Communications

RDT researched potential external stakeholder organizations actively involved in RDDD. The ensuing interviews focused on collecting perspectives from nine randomly selected individuals from representative organizations (see Appendix B: Stakeholders and Nominating Umbrella Organizations). The project team (1) determined stakeholder categories to facilitate data collection and analysis; (2) identified potential interview participants; and (3) determined the composition of the nine interviews across the categories. The project team used Microsoft Excel to randomize the 64 nominees received by the rare disease umbrella organizations. After completing the selection process, the project team performed outreach using targeted email communications.

To extend the reach of the RDDD community engagement and broaden the perspectives captured, the project team posted a docket for public comment on regulations.gov. Throughout the docket comment period, spanning four months, the team reviewed and incorporated insights into the DCI.

Develop Interview Guides and Docket Language
The project team created the external interview guide (see Appendix C: External Interview Guide) with the following objectives:

- Develop a detailed understanding of currently available resources for rare disease drug researchers and developers
- Identify challenges in bringing rare disease drugs to market; and
- Identify regulatory topics that could benefit from the creation or enhancement of RDDD curriculum

The project team organized the external interview guide into six RDDD core topics:

- Nonclinical
- Dose-finding
- Natural history studies and registries
- Novel endpoint and biomarker development
- Clinical trial design and analysis
- RDDD regulatory considerations

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[4] Docket (FDA-2022-N-3226)

Similarly, the docket was designed to capture the external RDDD community's understanding and need for educational materials on the above topics (see Appendix D: Docket Description).

Create a Data Collection Instrument (DCI)

To facilitate the collection of data and qualitative analysis of themes gleaned from interviews and docket comments, the project team developed a DCI to collate the qualitative data. The DCI served as the team's centralized tool for tracking engagement and synthesizing the data collected from both RDDD community engagement channels.

Collect and Analyze Data

The Agency used an independent contractor to facilitate focus groups and interviews. The team used a qualitative research approach to collect interview feedback. A general moderator guide was developed to assist the project team in facilitating the discussion. To provide participants with an opportunity to prepare for the interviews, RDT distributed a participant guide in advance. The moderator initiated the interviews by asking participants to provide insight into their professional background and expertise and asked questions by interviewee preference. This approach allowed the team to collect a detailed understanding of the experiences and perspectives reflected in participant responses and ensured that the topics in which participants were most experienced in were discussed first. For all interviews completed, there was at least one moderator facilitating the discussion and one team member capturing detailed notes to inform the interview feedback analysis. In total, the project team received input from representatives of nine external stakeholder organizations and 24 docket submissions.

To facilitate data collection, coding, and analysis the project team assigned categories to the interviewees and docket respondent organizations (see Table 1). Docket responses with feedback pertinent to educational materials for RDDD were analyzed and coded in the DCI. Comments that did not provide recommendations for educational materials or elucidate knowledge gaps were captured in the DCI but were not included in the analysis[5] (18 of the 24 docket submissions were included in the analysis).

Table 1: External Stakeholders

Stakeholder Category	Description
Industry	Includes the following: • Small-to-Medium Pharmaceutical Companies • Large Pharmaceutical Companies • Contract Research Organizations (CROs) • Professional Trade Organizations (PTOs)
Academia	Includes the following: • Academics • Clinicians or clinician/scientists
Patient Advocacy	Includes the following: • Patient Advocacy Groups (PAGs)

Generate Findings and Recommendations

Using the collated feedback from the interviews and docket, RDT identified: (1) opportunities to develop educational materials; (2) trends in perceived challenges experienced within and across

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[5] For example, comments advocating for policy changes such as reimbursement models for rare disease therapies were excluded from the analysis as they did not contain recommendations for rare disease curriculum or indicate RDDD knowledge gaps.

stakeholder categories; (3) resources stakeholders currently use to assist in overcoming these challenges (e.g., existing educational resources); and (4) recommendations for new resources to assist in overcoming existing challenges.

The project team analyzed interview responses and the docket comments to elucidate shared themes utilizing techniques, such as clustering. Based on this analysis, the project team evaluated responses to distinguish whether they could be addressed through the development of targeted educational materials or through other activities that would complement the LEADER 3D initiative (e.g., development of an external webpage for RDDD resources, or updating an existing webpage [i.e., CDER ARC] to be a central location for rare disease information). Recommendations for additional opportunities to empower rare disease drug developers are outlined in Appendix F.

IV. FINDINGS

Findings in this report were derived from expert insights obtained through interviews and docket comments from external stakeholders. Findings are organized by six RDDD topics: (1) nonclinical, (2) dose-finding, (3) natural history studies and registries, (4) novel endpoint and biomarker development, (5) clinical trial design and analysis, and (6) RDDD regulatory considerations.

A.   Overview of Findings and Recommendations

Table 2 provides a high-level overview of the assessment findings and common themes to inform FDA CDER's development of future educational materials and dissemination strategy. Findings and recommendations are divided into six RDDD topics.

Table 2: Challenges for External Stakeholders and Recommendations for RDDD

Challenges for External Stakeholders	Third Party Recommendations for RDDD
Nonclinical	
• Academics design nonclinical studies years before the design of clinical trials. Academics may have limited information and understanding on the design of appropriate experiments for the collection of data to support clinical studies for regulatory approval • Limited availability of suitable animal models and paucity of published literature on animal models for many rare diseases	• Develop and disseminate curriculum specifically targeted toward academics that demonstrates the regulatory value of nonclinical studies, including use cases and applicability • Enhance and/or develop and distribute resources (e.g., position papers, workshops) and relevant guidance documents to academics and clinical research networks on the use of non-animal model nonclinical methods to support rare disease drug applications
Dose-Finding	
• Difficulty in designing adaptive clinical trials to optimize dosing while balancing efficacy and adverse events for rare diseases with small and heterogenous patient populations, especially pediatric populations	• Provide best practices on developing a dose selection strategy for clinical trials enrolling small patient populations through workshops and/or guidance documents • Develop and share educational materials explaining how sponsors may use adaptive trial designs to determine dose selection while performing safety and efficacy studies, including extrapolating clinical data from adult to pediatric populations as appropriate

Challenges for External Stakeholders	Third Party Recommendations for RDDD
Natural History Studies and Registries	
• Varied awareness of the requirements for collecting natural history study data resulting in insufficient regulatory rigor of the natural history data	• Develop educational materials highlighting when and how an external control group can be appropriately used in clinical trial design • Promote existing draft Natural History Study guidance[6] and publish final guidance
Novel Endpoint and Biomarker Development	
• Uncertainty in determining whether a biomarker under development is relevant to demonstrating clinical efficacy for use as a surrogate endpoint • Difficulty utilizing common endpoints or developing novel endpoints to demonstrate clinical benefit for the rare disease when there is no existing therapy or a poor understanding of the disease progression • Sponsors with less experience developing endpoints encounter challenges finding and understanding FDA resources on endpoint development	• Provide clarification on the different types of endpoints (e.g., surrogate, composite) and the types of data expected to support regulatory approval • Provide examples[7] or case studies where applications with novel endpoints have been approved by FDA • Increase public communications through position papers, FDA workshops, and publications on novel endpoints (e.g., Rare Disease Endpoint Advancement pilot program)
Clinical Trial Design and Analysis	
• Rare disease stakeholders feel that gold standard study designs (e.g., randomized controlled trials) and traditional statistical approaches are not optimal for rare disease challenges, such as small patient populations, heterogeneity, limited natural history data, and ability to run only a limited number of trials • Sponsors are hesitant to implement adaptive trial designs due to their perception of FDA position on these types of trials and greater risk they perceive by using these trial designs • Challenges with collecting and utilizing real-world data (RWD) consistently to support RWE for rare diseases (e.g., access to patient data) • Delay in clinical trials due to difficulty diagnosing rare diseases, enrolling patients, and ensuring diversity in study populations	• Provide FDA guidance document specifically on clinical trial design and statistical approaches pertaining to small patient population and variation due to heterogeneity observed in some rare diseases • Provide case studies on successful applications of innovative trial designs • Develop materials to help sponsors identify the circumstances where external data, (i.e., natural history studies or RWD) can replace or enhance the control arm in phase II or phase III clinical trials • Conduct FDA-facilitated workshops to share operational perspectives and lessons learned while conducting complex, innovative clinical trials, such as platform, umbrella, and basket trials
Rare Disease Drug Development Regulatory Considerations	
• Limited understanding of Accelerated Approval pathway for rare diseases	• Provide more detailed information on utilizing expedited programs for rare diseases

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[6] https://www.fda.gov/media/122425/download
[7] https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

B. Topics

1. Nonclinical

Stakeholders noted limited access to information on appropriate non-animal model nonclinical methods for rare diseases that do not have suitable animal models. They conveyed a reliance on published literature to find information on questions related to nonclinical drug development but identified a dearth of published literature on animal models for rare diseases which is mainly developed by academic researchers.

When providing insight on recommendations for improving information available to assist with nonclinical challenges, participants shared that it would be helpful to have guidance from the Agency on requisites that could acceptably substitute for animal studies. They noted the potential usefulness of a roadmap outlining the data required before going into clinical trials versus data[8] that can be generated at a later stage in the context of RDDD (i.e., what studies are required pre-phase III, versus what can be done in parallel during clinical trial or postapproval).

While the interviewees acknowledged that there are excellent existing guidance documents focused on the clinical phases for drug development, there seem to be fewer guidance documents for the preclinical phase of the drug development process. They recommended the Agency provide more clarity on nonclinical stages to potentially reduce reliance on animal models. In addition, it would be helpful for stakeholders to have more education on nonclinical studies for experiments to successfully transition from the bench to the clinic, citing situations where some drugs perform extremely well in animal studies but do not maintain a similar performance in humans. With the increase in development of alternative methods to animal testing, respondents expressed an interest in learning more information from the Agency on the use of alternative methods to support rare disease drug applications.

Rare disease drug developers expressed that they do not have a clear understanding of the available interactions with the Agency for nonclinical questions prior to the pre-Investigational New Drug (Pre-IND) Type B meeting. Moreover, stakeholders stated they lack a clear understanding of how much data are needed to assess whether a therapy is a strong candidate to move forward in drug development. Challenges exist for academics in how to ascertain the necessary data to generate for regulatory submissions (i.e., IND applications) and how to appropriately document these data (e.g., good laboratory practice considerations).

Stakeholders shared that nonclinical research remains siloed from the rest of the drug development process and some grantees, specifically academics, have limited understanding of the regulatory value of nonclinical studies. They further elaborated that academic grantees have limited awareness of the information and studies required for an IND package until they go through the process. They also noted that pre-IND meetings are important mechanisms for educating academic and clinical researchers on the drug development process.

During interviews, non-industry stakeholders felt that while FDA has many guidance documents on nonclinical studies, their perception was these documents are targeted towards industry even though non-industry stakeholders are heavily involved in nonclinical work. The stakeholders recommended that FDA develop materials specific to and conduct outreach targeted toward the academic community and those less familiar with regulatory standards and development.

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[8] https://www.fda.gov/media/119757/download

In addition, respondents expressed an interest in nonclinical workshops hosted by FDA and acknowledged the value of guidance documents and scientific publications from FDA, U.S. Government (USG) (e.g., NIH), and other trusted third-party partners.

2. Dose-Finding

Stakeholders acknowledged the difficulty in selecting the optimal dose that balances efficacy and adverse events for rare diseases, where the patient populations are small and heterogeneous; especially, in pediatric populations. They recommended FDA develop educational materials focused on dose selection strategies for clinical trials with few subjects enrolled, especially when the therapeutic index is narrow.

Stakeholders expressed appreciation for the flexibility in clinical dose-finding incorporated into operationally seamless trials. They specified that this flexibility enables faster progression between phase I and phase II of a trial. One stakeholder suggested FDA provide more educational materials showcasing this approach as acceptable in certain therapeutic areas and to encourage its use in others. They emphasized the benefit of having the ability to move smoothly from one phase of a trial to another, recognizing it as a positive step forward in accelerating drug development.

Stakeholders recommended that FDA provide specific and detailed information on the use of alternative and innovative approaches to evaluating dose-exposure and response relationships early in drug development to guide dose selection strategies for phase III trials. In addition, one stakeholder recommended that FDA provide information on how sponsors can use biomarker response to establish an appropriate dosing frequency. Several stakeholders suggested that FDA host workshops and publish guidance documents to highlight best practices to characterize the dose-exposure-response relationship, especially in cases with limited nonclinical data and a limited pool of trial participants.

The RDDD community also provided feedback on pharmacokinetics and pharmacodynamics (PK/PD) resources, requesting guidance specifically providing PK/PD comparability after formulation or process changes. They expressed the need for additional training related to PK studies and the use of modeling to significantly reduce the quantity of samples required for both preclinical and clinical studies.

In addition, stakeholders recommended that FDA develop educational materials explaining how sponsors may extrapolate clinical data from adult to pediatric populations and provide considerations informing when pharmacokinetic (PK)-only bridging from adult population to specific pediatric subgroups may be appropriate.

3. Natural History Studies and Registries

Stakeholders expressed common difficulties with the use of natural history studies and registries in cases where certain rare diseases have a higher interest in the broader community, resulting in various potential treatments under development and only a small subset of patients available to study. This constraint can result in difficulties finding *de novo* patients who can provide new data points. Another challenge identified, related to the impact that changes in standard of care had on natural history study data over the period the natural history study was conducted. In such cases, for example, where standard of care changes before the clinical study initiation, it is difficult to determine the quality of the natural history study data, and therefore, its appropriateness to be used as an external control. Such situations can contribute to the data not meeting FDA standards for regulatory use. The RDDD community opined that data sharing could help alleviate some of

these issues (e.g., the C-PATH Rare Disease Cures Accelerator-Data and Analytics Platform[9]) but were aware this was outside FDA's regulatory purview.

Industry stakeholders indicated they obtain natural history and registry data through outreach and partnership with PAGs, and they voiced challenges with the perceived lack of regulatory rigor in natural history data, noting these studies are usually led by members of academia who may be less familiar with regulatory standards. This sentiment was further bolstered by academic and clinical stakeholders sharing they did not know how to define and/or assess the regulatory readiness of natural history data. PAG stakeholders recognized their organizations play an important role in facilitating the development of registries and natural history studies; however, they observed that many PAGs do not have the appropriate financial resources or in-house regulatory expertise. As a result, PAGs may design registries that do not collect the information FDA requires for regulatory approval.

Stakeholders also conveyed a desire for further guidance on the use of natural history and registry data and specific case studies explaining when and how an external control group can be appropriately used. They further highlighted the extensive efforts required from PAGs and academia to gather natural history data, underscoring the importance of funding programs such as FDA's Natural History Studies Grants Program.[10]

Interviewees expressed that the unique challenges of each rare disease creates barriers to collecting and applying natural history and registry data for RDDD programs, but had favorable views of the FDA's draft guidance titled, "Rare Diseases: Natural History Studies for Drug Development"[11] for aiding in the development of these natural history programs. They highlighted a need for more education and clarification on appropriate, acceptable uses of natural history studies to support drug application approvals. They noted a desire for FDA to clarify how RWD from natural history studies can be utilized as a source of RWE as the use of different data sources continues to expand.

Stakeholders also noted a final guidance does not yet exist, and they perceive the existing draft guidance as outdated. For example, they stated prospective natural history studies are not always feasible due to the rapidly evolving treatment landscape for certain rare diseases. They stressed the importance of leveraging existing data and improving data collection going forward, despite changes in scientific understanding. Stakeholders also shared that in this guidance, FDA emphasizes that drug development should not be delayed due to a lack of natural history data.

Interviewees shared that information presented as case studies and best practices will help groups (e.g., PAGs) that may not have as much drug development experience but who fund many natural history studies and registries. Along with case studies, the participants stated it is useful when FDA presents examples on how to utilize natural history studies at conferences and webinars that reach the scientific community. They also noted an interest in having insight into how the Agency looks at global registries for FDA-sponsored trials and collaborates with other regulatory organizations regarding these data.

Stakeholders also shared their awareness of the draft guidance titled, "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products." [12] Respondents suggested the development of FDA case studies to provide illustrative examples on when an external control group using natural history data or RWD is appropriate. They further outlined the utility in having the Agency's thoughts on approaches and tools to support the

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[9] https://c-path.org/programs/rdca-dap/
[10] https://www.fda.gov/industry/clinical-trial-and-natural-history-study-grants
[11] https://www.fda.gov/media/122425/download
[12] https://www.fda.gov/media/164960/download

development of databases or for the conduct of natural history studies to support regulatory decision making.

Another respondent noted FDA could provide additional guidance to sponsors about RWE that is fit-for-purpose and constitutes regulatory-grade data. They indicated sponsors would benefit from clearer communication, criteria, and examples of data requirements for specific disease states that would enable sponsors to collaborate with data providers upfront to ensure the data collected are fit-for-purpose. The Agency could also consider partnering with source data providers to set and establish expectations for regulatory quality datasets and provide more transparency about how data are currently being evaluated by reviewers (e.g., C-PATH Rare Disease Cures Accelerator-Data and Analytics Platform [RDCA-DAP]).

4. Novel Endpoint and Biomarker Development

The RDDD community highlighted several challenges related to the development of novel endpoints and biomarkers. They identified the need for additional clarification on evaluating clinically meaningful changes for endpoints and biomarkers as well as data requirements for each type of endpoint (e.g., single-measure, composite, multicomponent, intermediate, surrogate).

In addition, interviewees cited challenges with composite biomarker panels due to the heterogeneity associated with certain rare diseases and the difficulty in identifying a single biomarker that can accurately predict treatment response in all patients. This challenge is further compounded by the limited natural history data available and the complex relationship between various biomarkers and disease progression. Therefore, stakeholders perceive a causality dilemma with respect to endpoint validation, stating difficulty in determining which should come first: the validation of a single endpoint or the validation of multicomponent endpoints.

Furthermore, stakeholders opined that limited sample sizes associated with RDDD create challenges in developing robust statistical analysis of endpoints and expressed a desire for FDA to provide clarity on what constitutes an adequate therapeutic response.

During the interviews, both experienced and inexperienced (in rare disease drug development) stakeholders noted challenges with endpoints in RDDD: they acknowledged the vast amount of endpoint information available, while at the same time feeling overwhelmed when trying to locate specific information related to RDDD. Despite the availability of FDA's Biomarker Qualification: Evidentiary Framework[13] draft guidance, which stakeholders identified as a good resource, they also shared that the process of developing and validating endpoints is not straightforward. They expressed a desire for FDA to develop more materials to elucidate the process for endpoint and biomarker development. The respondents felt that FDA could consider providing more information on the development and acceptance of novel surrogate endpoints, particularly for clinically heterogenous, slowly progressive rare diseases. In addition, stakeholders requested clarity from FDA on the type of evidence needed to support the use of surrogate endpoints. Stakeholders mentioned a need for a framework outlining new criteria for the qualification and validation of surrogate endpoints in RDDD. They also emphasized a need for guidance on multicomponent endpoints, while some stakeholders were unaware of the Multiple Endpoints in Clinical Trials final guidance.[14]

Respondents suggested FDA consider providing information on innovative approaches for novel endpoint development and validation (e.g., approaches for the use of nonclinical data, in silico data, and artificial intelligence [AI]) and include case studies on alternative approaches to

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[13] https://www.fda.gov/media/122319/download
[14] https://www.fda.gov/media/162416/downloadI

validating COAs for patients living with rare diseases. A stakeholder requested a guidance document to inform the updating or retrofitting of an existing COA tool found within the COA compendium to validate a tool for use in a rare disease with symptoms similar to those of the disease for which the original tool was developed. These topics have been addressed in the recent PFDD guidance on Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments – a request suggesting there is varied or limited awareness of existing guidance documents available. To further aid in endpoint development, respondents suggested FDA develop educational materials to identify the appropriate qualitative research methods sponsors should use to properly obtain patient input. They also added that these materials should include a discussion on how to interpret the meaningfulness of change or absence of change within these rare disease populations.

Stakeholders highlighted the importance of early engagement with FDA to discuss potential endpoints and biomarkers, emphasizing the need for de-risking choices and removing hurdles in the development process. However, they found it difficult to ascertain when they had sufficient data to meet with FDA. Furthermore, the stakeholders acknowledged the opportunities presented by the novel meeting types under PDUFA VII (e.g., Initial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meetings); however, interviewees had varied levels of awareness of FDA's RDEA Pilot Program, which enables earlier conversations with FDA to accelerate drug development programs with high unmet medical needs. They expressed positive experiences with Type D meetings and looked forward to working with the Agency to improve communications and identify additional avenues for discussions.

Stakeholders also suggested the need for additional opportunities to conduct scientific dialogue with FDA. They expressed an interest in having mini workshops with external key opinion leaders (KOLs) to facilitate holistic scientific discussions on specific diseases.

Overall, the stakeholders requested additional information from FDA on combining biomarkers, COAs, validation of endpoints, and other composite tools to help sponsors develop innovative endpoints for efficacy and safety.

5. Clinical Trial Design and Analysis

Concerns with patient recruitment were common among interviewees, and the RDDD community noted that they encountered reluctance from patients to participate in placebo-controlled trials (i.e., the risk of being randomized into the placebo group). Participants indicated education efforts should target not only drug developers, but also patients and clinicians involved in RDDD due to the challenges associated with patient recruitment and delays in rare disease diagnosis. Some stakeholders identified disease diagnosis and patient stratification as the primary challenges regarding clinical trial design and RDDD. In addition, participants opined on challenges related to enrollment associated with the limitations of double-blind, placebo controls for RDDD, endpoint selection, clinical trial diversity requirements, and the use of RWD/RWE in clinical trials.

Given the perceived challenges in conducting a RCT in rare disease populations, the RDDD community stated they could benefit from receiving more information on adaptive trial designs and noted hesitancy from sponsors to implement adaptive trials. Participants felt they did not have enough guidance on the types of FDA-acceptable adaptive clinical trial designs and opined it was an educational knowledge gap the Agency may wish to address. In addition, several participants observed that academics and clinicians have limited knowledge of adaptive clinical trial designs and analysis and depend on pharmaceutical partners to serve as their educational resource and to execute the work. They also expressed challenges finding guidance documents specific to a certain clinical study design challenge and relevant examples of novel and innovative designs that demonstrate substantial evidence effectiveness.

While most interviewees were aware of existing guidance documents and resources available to assist with clinical trial design and acknowledged there are many FDA resources for this topic, many requested additional resources specific to RDDD. For example, they cited the FDA guidance on Adaptive Designs for Clinical Trials[15] and indicated they would appreciate a rare disease-specific guidance on seamless design protocols. Participants requested FDA guidance specifically on clinical trial design and analysis involving small populations and indicated that current methods are not optimal for small trial populations and the variation due to heterogeneity observed in some rare diseases. They also suggested the Agency consider developing materials to help sponsors identify the circumstances where external data (i.e., natural history studies or RWD) can replace or enhance the control arm in phase II or phase III clinical trials. In addition to FDA guidance documents, the RDDD community cited FDA's summary of approvals as a helpful resource to provide precedent in their processes and indicated a need for case study examples that provide specific information for RDDD.

Most participants indicated gaps in their understanding of statistical and model-based approaches and expressed a need for additional information from FDA. They requested guidance on unique statistical approaches for rare disease clinical trials that provide information on model-informed drug development[16] to overcome common RDDD limitations (e.g., small patient sample size, general lack of natural history data, and small patient populations). Participants suggested developing materials on unbalanced drug to placebo randomization, external or simulated controls, use of RWE, use of Bayesian statistical models, and other approaches to compensate for limited sample sizes.

They indicated a desire for FDA to provide more information on expedited programs to the public (e.g., accelerated approval program, breakthrough therapy designation, fast track designation, and priority review designation); they noted that while they are aware of expedited programs, they are not familiar with the details and processes associated with these pathways. Providing further clarification could facilitate more informed discussions among sponsors and stakeholders when exploring the feasibility of accelerated approval.

Participants mentioned leveraging the Complex Innovative Trial Design (CID) pilot meeting program[17] to mitigate risks and establish a collaborative relationship with reviewers. They emphasized the need for educational materials to communicate insights from the CID pilot program and disseminate learnings specific to rare disease indications. They believed such materials could inform and influence approaches in other therapeutic areas and help sponsors navigate similar design challenges prior to engaging with the Agency.

6. Rare Disease Drug Development Regulatory Considerations

The RDDD community had a varied perspective on the understanding of regulatory concepts for RDDD. Most participants expressed a desire for more direct engagement with FDA to receive regulatory support. They stated these interactions could save time, prevent confusion, and provide more opportunities for open dialogue to avoid unnecessary research and data collection.

The RDDD community also requested more clarity on FDA's Accelerated Approval pathway and a comment from the docket stated, "FDA's expedited programs including Accelerated Approval, Fast Track Designation, Breakthrough Therapy Designation, Priority Review Designation, and Regenerative Medicine Advanced Therapy (RMAT) Designation are important tools in advancing efficient and innovative drug development and should be promoted by the Agency as such... [we]

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[15] https://www.fda.gov/media/78495/download
[16] https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program
[17] https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

recommend FDA provide additional information on considerations regarding the use of expedited programs for rare disease products."

Rare disorders are unique, which makes it challenging for the Agency to develop disease-specific guidance documents. The participants shared that the existing guidance documents often are not specific to RDDD, which necessitates discussion meetings with the Agency to address complex questions and determine a path forward. They encouraged FDA staff to continue presenting at conferences and providing insights through published papers, as it helps to set expectations across therapeutic areas and promotes a better understanding of the Agency's regulatory perspective. The RDDD community highlighted the importance of engaging with trade associations and patient groups to facilitate regulatory discussions and foster the connection between FDA and the patient community. They advocated for FDA to disseminate illustrative case studies showcasing FDA's rationale.

PAGs indicated that academics primarily use PubMed to search for resources to answer questions regarding RDDD and noted FDA guidance documents are not published on this platform. To this end, they recommended academics likely need to be informed and educated on how to find resources on FDA's website that will help during their preclinical research (e.g., conducting animal studies). PAGs also reiterated that their stakeholders' (e.g., patients and families, researchers, and advisory committees) limited or lack of understanding of the regulatory process creates a barrier to championing the development of rare disease drugs. PAGs observed their stakeholders often learn about the intricacies of the regulatory process when an IND is placed on hold and felt educational materials could promote increased transparency on the regulatory process.

C. Existing FDA Resources Applicable to Rare Disease Drug Development

Overall, the RDDD community emphasized the need for clear and consistent communication from FDA, both in written feedback and through public presentations, to ensure alignment between conference discussions, guidance documents, and regulatory decision making. The RDDD community felt that having an early discussion with FDA will help the sponsors establish enough evidence for approval. The project team's findings also elucidated that interviewees experienced challenges in finding existing resources or they were unaware of existing resources prompting them to recommend the development of materials that are currently available on the public FDA website. Table 3 lists existing FDA resources (e.g., guidance documents, webpages, and programs) that are applicable to RDDD.

Table 3: Existing FDA Informational Resources by Rare Disease Topic Area

Topic(s)	Corresponding Existing FDA Resource
Natural History Studies and Registries; Nonclinical; Novel Endpoint and Biomarker Development	• Rare Diseases: Considerations for the Development of Drugs and Biological Products Guidance • Critical Path Innovation Meetings Website • Rare Disease Endpoint Advancement Pilot Program Website
Rare Disease Drug Development Regulatory Considerations; Nonclinical; Clinical Trial Design and Analysis	• Investigational New Drug (IND) Application • Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings (Draft) • Investigational New Drug Application Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Chemistry, Manufacturing, and Controls Recommendations, Guidance for Sponsor-Investigators • IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations Guidance for Sponsor-Investigators • IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations • Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products • Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products: Guidance for Industry • Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases Guidance for Sponsor-Investigators • Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics • Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products • INTERACT Meeting Website • Support for clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program • Accelerating Rare diseases Cures (ARC) Program Website
Dose-Finding; Clinical Trial Design and Analysis	• General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry • E17 General Principles for Planning and Design of Multi-Regional Clinical Trials • Model-Informed Drug Development Paired Meeting Program
Natural History Studies and Registries	• Rare Diseases: Natural History Studies for Drug Development (Draft) • Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products • Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products • Real World Data / Real World Evidence RWD/RWE • Center for Biologics Evaluation and Research & Center for Drug Evaluation and Research Real-World Evidence • Real-World Data: Assessing Registries To Support Regulatory Decision-Making for Drug and Biological Products

Topic(s)	Corresponding Existing FDA Resource
Novel Endpoint and Biomarker Development; Clinical Trial Design and Analysis	• Multiple Endpoints in Clinical Trials Guidance for Industry • Biomarkers, EndpointS, and Other Tools (BEST) Resource Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure • Clinical Outcome Assessment Compendium • CDER Pilot Grant Program: Standard Core Clinical Outcome Assessments (COAs) and their Related Endpoints • Rare Disease Cures Accelerator • FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making Webpage • Patient-Focused Drug Development: Collecting Comprehensive and Representative Input • Patient-Focused Drug Development: Methods to Identify What Is Important to Patients • Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments • Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making • Qualification Process for Drug Development Tools • Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure
Clinical Trial Design and Analysis; Natural History Studies and Registries	• Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products • Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence

V. CONCLUSIONS AND CONSIDERATIONS

Conclusions are derived by an independent third-party contractor from interviews with the external RDDD community as well as comments collated from an FDA public docket. The conclusion includes recommendations on applying the findings to the development of public-facing educational materials to support RDDD.
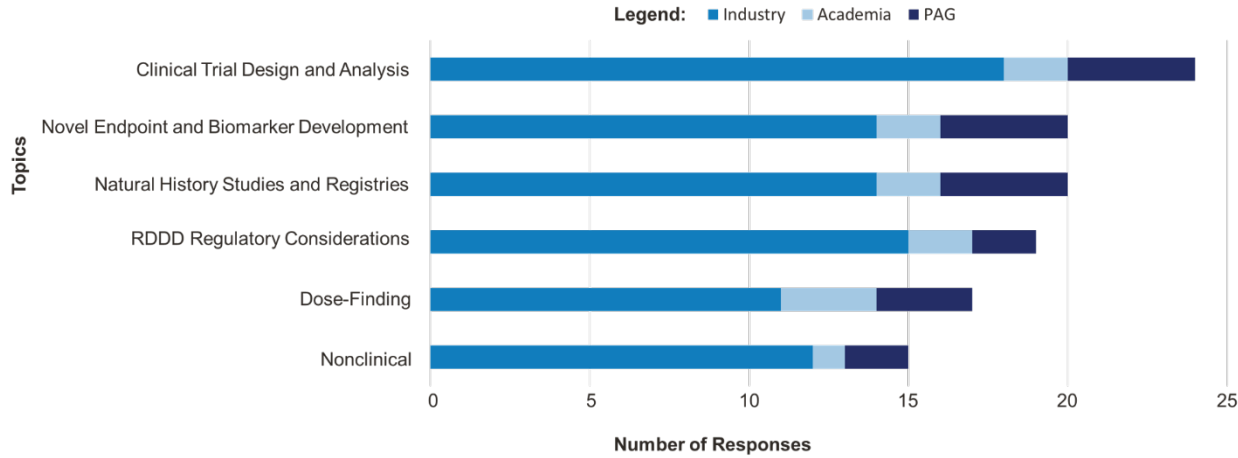

Figure 1: RDDD Community Comments by Topic

The project team employed several engagement mechanisms to understand perceived challenges in rare disease drug development, including interviews, and collection of feedback through docket comments from the RDDD community. Analysis of the qualitative data collected, together with the recommendations made by RDDD community outlined in the Overview of Findings and Recommendations section above, suggest to the Agency that there are opportunities to (1) enhance its communication strategies to target and amplify messaging toward multiple and specific RDDD stakeholders (e.g., academics involved in the development of rare disease drugs); (2) develop new educational materials where existing materials are lacking regarding design and conduct of rare disease clinical trials helpful to the RDDD community and (3) design a central hub for RDDD (e.g., the CDER ARC webpage) to provide rare disease drug developers with a centralized location for existing and new resources. The considerations for these findings are as follows:

(1) The project team identified salient RDDD topics that could benefit from further curriculum development. These were: (1) clinical trial design and analysis, (2) novel endpoint and biomarker development, (3) natural history studies and registries, and (4) RDDD regulatory considerations, as illustrated in Figure 1 above identified by stakeholders.

(2) This discrete stakeholder engagement and analysis endeavor also characterized the lack of visibility of existing FDA resources; and also an opportunity for the Agency to augment its communication strategies to target and amplify messaging toward specific RDDD stakeholders.

(a) The project team received recommendations through interviews and docket comments that are complementary to the LEADER 3D project objectives. Several members of the RDDD community expressed an interest in establishing a structured, centralized repository dedicated to FDA RDDD resources and programs. In response to this input, ARC program staff re-organized its web page[18] and created a repository of rare disease educational resources and workshops in addition to the future materials generated from LEADER 3D. This repository includes links to various workshops, a list of rare disease-relevant guidance documents organized by topic, and a list of RDDD funding opportunities (those resources can be found at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program).

(b) Communication strategies could be developed to target specific stakeholders to increase awareness of available FDA resources. For example, through stakeholder interviews the project team learned academics rely on resources in the form of peer-reviewed publications (e.g., PubMed articles) and are less aware of FDA resources meant to provide regulatory guidance for rare disease drug development programs. Enhancing communication strategies for academic stakeholders may increase awareness of such resources.

Additional recommendation that are out of scope for this phase of the LEADER 3D initiative are summarized in Future Opportunities to Empower Rare Disease Drug Developers (Appendix F).

The CDER ARC program provides strategic governance and coordination of the Center's rare disease activities, and LEADER 3D has been a paramount mechanism through which CDER's RDT has engaged with those involved in the design and conduct of rare disease clinical trials to better understand and address the challenges in bringing safe and effective drug and biological products to market for patients with rare diseases.

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[18] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program

VI. APPENDIX

This section includes (1) a glossary containing the acronyms used in this document along with the corresponding definition, (2) participating RDDD community organizations and nominating umbrella organizations, (3) external interview guide, (4) docket language, (5) resources referenced during interviews, and (5) a list of additional insights and future potential LEADER 3D opportunities.

A.   Glossary

Acronyms	Definition
AI	Artificial Intelligence
ARC	Accelerating Rare disease Cures Program intended to leverage CDER's collective expertise to provide strategic coordination of the Center's rare disease activities
ASGCT	American Society for Cell and Gene Therapies
ASO	Antisense Oligonucleotides
CBER	Center for Biologics Evaluation and Research, a center within the U.S. Food and Drug Administration
CDER	Center for Drug Evaluation and Research, a center within the U.S. Food and Drug Administration
CID	Complex Innovative Trial Design
CMC	Chemistry, Manufacturing, and Control
COA	Clinical Outcome Assessment
C-PATH	Critical Path Institute
CRO	Contract Research Organization
DCI	Data Collection Instrument
FDA	U.S. Food and Drug Administration, an agency within the U.S. Department of Health and Human Services
FOIA	Freedom of Information Act
FOP	Fibrodysplasia Ossificans Progressiva
GMP	Good Manufacturing Practices
IND	Investigational New Drug
IQ	Innovation & Quality
KOL	Key Opinion Leader
LEADER 3D	Learning and Education to ADvance and Empower Rare Disease Drug Developers
NORD	National Organization for Rare Disorders
PAG	Patient Advocacy Groups
PCORI	Patient-Centered Outcomes Research Institute
PD	Pharmacodynamic
PDUFA	Prescription Drug User Fee Act

Acronyms	Definition
PFDD	Patient Focused Drug Development
PhRMA	Pharmaceutical Research and Manufacturers of America
PK/PD	Pharmacokinetic and Pharmacodynamic
PRA	Paperwork Reduction Act
PROM	Patient-Reported Outcomes Measurements
PTO	Professional Trade Organizations
Q&A	Question and Answer
RCT	Randomized controlled trial
RDCRN	Rare Diseases Clinical Research Network
RDDD	Rare Disease Drug Development
RDEA	Rare Disease Endpoint Advancement
RDT	Rare Diseases Team (organizationally aligned to FDA/CDER/OND/ORDPURM/DRDMG)
RMAT	Regenerative Medicine Advanced Therapy
RWD	Real-World Data
RWE	Real-World Evidence

B. Stakeholders and Nominating Umbrella Organizations

Table 4: External Stakeholder Nominating Umbrella Organizations

No.	Institution/Company	Nominating Organization	Category
1	University of Cincinnati	Rare Diseases Clinical Research Network (RDCRN)	Academia 1 (of 1)
2	NDA Partners	American Society of Gene and Cell Therapy (ASGCT)	CRO 1 (of 2)
3	Syneos Health	Association of Clinical Research Organizations (ACRO)	CRO 2 (of 2)
4	Roche/Genentech	Biotechnology Innovation Organization (BIO)	Large Pharma 1 (of 1)
5	Cure Sanfilippo Foundation	EveryLife Foundation for Rare Diseases (ELF)	PAG 1 (of 2)
6	International Fibrodysplasia Ossificans Progressiva Association	National Organization for Rare Disorders (NORD) Corporate Council	PAG 2 (of 2)
7	Amicus Therapeutics	EveryLife Foundation for Rare Diseases (ELF)	Small-to-Medium Pharma 1 (of 3)
8	Rallybio	Biotechnology Innovation Organization (BIO)	Small-to-Medium Pharma 2 (of 3)
9	BridgeBio	Biotechnology Innovation Organization (BIO)	Small-to-Medium Pharma 3 (of 3)

Table 5: U.S. Government Agencies and Institutes

Participant Institute/Program

NIH:
- National Center for Advancing Translational Sciences (NCATS)
- National Center for Complementary and Integrative Health (NCCIH)
- National Eye Institute (NEI)
- National Human Genome Research Institute (NHGRI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute of Arthritis and Musculoskeletal and Skin (NIAMS)
- National Institute of Child Health and Human Development (NICHD)
- National Institute of Neurological Disorders and Stroke (NINDS)

Department of Defense (DoD):
Congressionally Directed Medical Research Programs (CDMRP)

C.   External Interview Guide

External Interview Guide

I.   BACKGROUND
 	
The Center for Drug Evaluation and Research (CDER) Rare Diseases Team (RDT), at the U.S. Food and Drug Administration (FDA) is working with an independent contractor, to facilitate, support, and accelerate the advancement of drug and biologic products for patients with rare disorders through the development and dissemination of educational materials for rare disease drug developers. In May 2022, CDER established the Accelerating Rare diseases Cures (ARC) program to prioritize stakeholder engagement and development of infrastructure to encourage innovation and mitigate challenges impacting rare disease drug development. To support this mission, the independent contractor is interviewing rare disease drug development stakeholders to better understand the unique challenges in bringing rare disease products to market and identify regulatory topics that could benefit from the creating or expanding educational materials. The findings of this analysis may be used to inform the enhancement of educational materials for stakeholders actively involved in rare disease drug development.
 	
II.   DISCUSSION QUESTIONS
 	
    A.   NONCLINICAL
 	
        1.   What are your thoughts on working with the FDA and/or materials available by FDA regarding the design and conduct of nonclinical studies for a rare disease therapy?
 	
    B.   NATURAL HISTORY STUDIES AND REGISTRIES
 	
        1.   What are your thoughts on working with the FDA and/or materials available by FDA when preparing to use natural history and registry data as part of a regulatory package to support a marketing application?
 	
    C.   NOVEL ENDPOINT AND BIOMARKER DEVELOPMENT
 	
        1.   What are your thoughts regarding working with the FDA and/or materials available by FDA when developing clinical trial endpoints and novel endpoints (e.g., biomarkers, clinical outcome assessments, other) to support a marketing application?
 	
    D.   CLINICAL TRIAL DESIGN AND ANALYSIS
 	
        1.   What are your thoughts on working with FDA and/or materials available by FDA in designing adequate and well-controlled trials (e.g., clinical trial design, statistical approaches, complex and innovative design features, etc.)?
 	
    E.   DOSE-FINDING
 	
        1.   What are your thoughts on working with FDA and/or materials available by FDA when determining dose-finding strategies in clinical trials?
 	
    F.   RARE DISEASE DRUG DEVELOPMENT REGULATORY CONSIDERATIONS
 	
        1.   What are your thoughts on working with the FDA and/or materials available by FDA when determining what information (e.g., efficacy data, safety data, confirmatory evidence, benefit-risk assessment, etc.) will support a marketing application that demonstrates substantial evidence of effectiveness for a rare disease therapy?
 	
    G.   CLOSING QUESTION
 	
        1.   Are there any questions within these topics you feel need to be addressed that we haven't touched on today?

D.   Docket Description

LEADER 3D: Docket Description

Title: Opportunity for Feedback on Development and Dissemination of Educational Materials on Rare Disease Drug Development

The combination of government incentives and scientific advancements has provided momentum for the development of rare disease treatments, including treatments that can impact disease trajectory.

However, there remains a tremendous unmet need for FDA approved therapies for rare diseases that affect between 25 and 30 million Americans. This means that about 1 in 10 Americans have a rare disease. Approximately half of those affected by rare diseases are children. Of these rare diseases, the vast majority have no treatment.

Developing a rare disease treatment is challenging. To this end, the Center for Drug Evaluation and Research's Accelerating Rare disease Cures (ARC) Program is initiating "Learning and Education to Advance and Empower Rare Disease Drug Developers" (LEADER 3D) to facilitate the development of safe and effective drugs to treat rare diseases. One aspect of the multifaceted challenges involves identifying knowledge gaps regarding rare disease drug development and related regulatory topics. CDER is seeking input to help identify and create resources to fill the knowledge gaps. Potential topics include:

- Nonclinical and clinical pharmacology considerations
- Clinical trial design and interpretation
- Regulatory considerations for rare disease drug development

With input from rare disease stakeholders who design and conduct rare disease drug development programs (academics, industry, patient groups, other federal partners, etc.), FDA believes we can better understand and address knowledge gaps for external stakeholders. Input on this topic will be used to help inform the development of publicly available educational materials, such as informative videos.

Through the development of additional resources, we are working to support our common goal of accelerating the availability of safe and effective treatments for rare diseases. For input to be considered for this initiative, please provide your comments by April 30, 2023.

E. Informational Resources Referenced During Interviews

Stakeholder Group	Resource Referenced
Industry	• Critical Path Institute (C-PATH)[19] • FDA's summary of approvals[20] • FDA's guidance on endpoints[21] • Obtaining information from a public domain website • Leveraging the existing relationship with a Center and/or Office • Type B and C meetings (e.g., for nonclinical discussions and question about statistical approaches) • Type D meetings • New alternative methods program[22] • Scientific publications from FDA reviewers or trusted third-party partners to guide the approach to the drug development process • The Rare Diseases: Natural History Studies for Drug Development Draft Guidance for Industry [23] • The Accelerated Approval Program[24] • Leveraging opportunities presented by the novel meeting types under PDUFA VII • Rare Disease Endpoint Advancement (RDEA) Pilot Program[25] • Draft guidance: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products[26] • Complex Innovative Trial Design (CID) Meeting Program[27] • Draft guidance Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products[28] • The anticipated guidance on Accelerated Approval and clinical trial diversity provisions outlined in Food and Drug Omnibus Reform Act of 2022 (FDORA) (Federal Drug and Cosmetic Act) • FDA conferences and webinar presentations on natural history studies • Upcoming, unpublished article from University of California, Berkley including a roadmap for the use of RWE consolidating FDA documents into a streamlined process to help rare disease drug developers use RWE • U.S. Neuromuscular Disease Registry as a case study for how registries can be developed and used (i.e., accessing 150 data hubs [hospitals] and creating a database to use as a registry) • Patient-Centered Outcomes Research Institute (PCORI) • American Society of Gene & Cell Therapy (ASGCT) • Other databases from non-FDA entities summarizing FDA information • Engaging with the Agency at conferences and symposia where specific questions can be asked

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[19] https://c-path.org/

[20] http://www.fda.gov/drugsatfda

[21] https://www.fda.gov/media/162416/download

[22] https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda

[23] https://www.fda.gov/media/122425/download

[24] https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

[25] https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program#:~:text=The%20RDEA%20Pilot%20Program%20is,the%20efficacy%20endpoint%20development%20process

[26] https://www.fda.gov/media/164960/download

[27] https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

[28] https://www.fda.gov/media/133660/download

Stakeholder Group	Resource Referenced
Academia	• FDA materials for standardized surveys and or quality of life metrics
PAGs	• The Rare Diseases: Natural History Studies for Drug Development Draft Guidance for Industry[29] • Biomarker Qualification: Evidentiary Framework[30]

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[29] https://www.fda.gov/media/122425/download
[30] https://www.fda.gov/media/122319/download

F. Future Opportunities to Empower Rare Disease Drug Developers

The interviews and docket comments provided the project team with additional observations, challenges, and additional recommendations beyond the LEADER 3D animated videos and case studies. The project team assessed the collection of stakeholder contributions and identified actionable insights that may prove beneficial for the Agency's consideration. Table 6 provides a summary of additional opportunities that may be used to inform future ARC program efforts.

Table 6: Additional Recommendations

Topic	Recommendation
General	• Utilize town hall events to present case studies in a webinar format
Nonclinical	• Publish formal guidance and/or nonbinding position papers from FDA elaborating on suitable alternatives to animal models (e.g., cell models) • Development of a database of validated, appropriate animal models for rare diseases • Provide additional clarity on the data sponsors need to collect in preparation for pre-IND and IND meetings to adequately support proposed endpoints
Dose-Finding	• Develop dose-finding case studies • Create educational materials for patients and families to explain dose-finding studies and the collection and use of natural history data and RWD
Natural History Studies and Registries	• Create case studies explaining when and how an external control group can be appropriately used • Publish more FDA guidance documents on diagnostic tools, including companion diagnostics • Establish an RWE task force to coordinate programs and activities within the Agency related to the collection and use of RWD/E for clinical trials
Novel Endpoint and Biomarker Development	• Create resources on novel endpoints and biomarkers with examples and case studies
Clinical Trial Design and Analysis	• Develop educational materials for clinicians and patients to improve patient enrollment for clinical trials • Provide FDA guidance on unique statistical approaches and model-informed drug development for small population sizes and lack of natural history data associated with rare diseases