2024 EVERYLIFE FOUNDATION SCIENTIFIC WORKSHOP

Therapy Development for Small Populations:

Evidence, Implications, & Policy in Characterizing Ultra-Rare

EVERYLIFE FOUNDATION FOR RARE DISEASES

Executive Summary

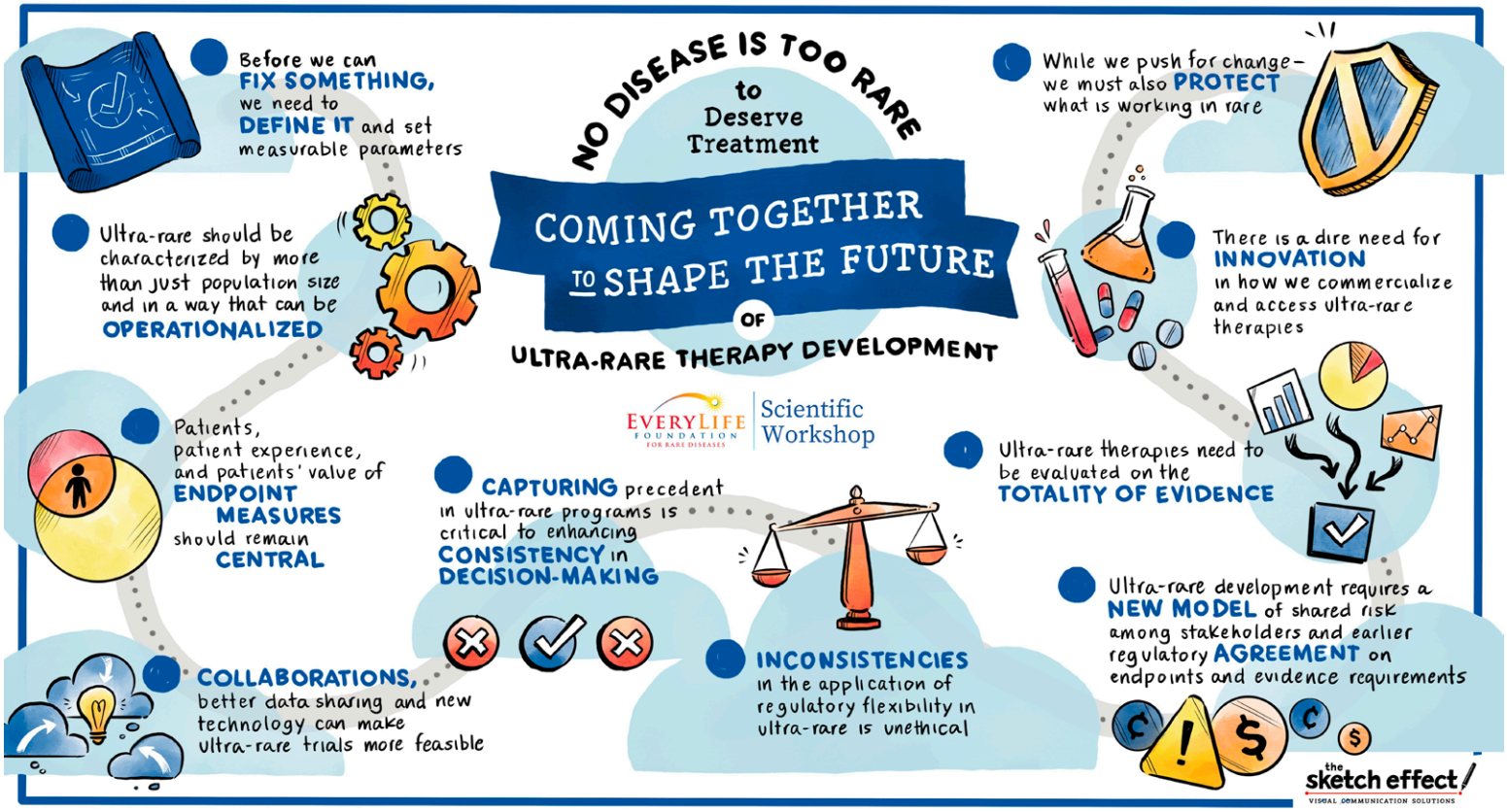
Despite significant improvement in the success of rare disease therapy development over the past four decades, the vast majority of rare diseases (95%) still lack FDA-approved therapies, and few of the therapies that have been approved are for ultra-rare diseases.

To address this issue, in May 2024, the EveryLife Foundation convened a workshop to discuss the considerations and implications of establishing a statutory definition for ultra-rare diseases. Subject matter experts from the U.S. Food and Drug Administration (FDA), the National Institutes of Health (NIH), patient advocates, drug developers, and academia came together to reflect on the current state of therapy development for very small, ultra-rare population diseases and identify opportunities.

Discussions centered around challenges faced by those in ultra-rare therapy development, most notably the extraordinary obstacles they face navigating the regulatory drug development lifecycle and meeting traditional standards for demonstrating safety and efficacy. Congress and the FDA have taken commendable steps over the past 40 years to bridge the gap between this standard and the realities of ultra-rare drug development. This includes permitting the use of surrogate biomarkers in accelerated approvals, facilitating the integration of the patient perspective into drug development processes, and creating programs to help rare disease therapy developers navigate the regulatory approval lifecycle. The FDA is also permitted the flexibility to exercise its scientific judgment in determining the kind and quantity of data a sponsor may provide to meet the statutory standard of substantial evidence.

However, discussions throughout the workshop revealed that regulatory flexibility hasn't yielded consistent results for patients, advocates, and drug developers of these ultra-rare diseases. The lack of regulatory precedent and consistency has also raised concerns that the application of flexibility in regulatory decision-making may be exacerbating inequities and introducing greater risk for drug developers.

There was strong support among workshop participants for creating a framework for ultra-rare diseases that will enable tailored solutions that address the unique challenges they face, particularly generating the evidence needed to meet current regulatory standards for demonstrating safety and efficacy. Throughout the day, many considerations beyond patient population size for developing a definition for "ultra-rare" diseases were discussed. Clinical trial design, access to care and clinical trials, ethical obligations, and regulatory opportunities emerged as primary themes. Discussions also included several potential policy changes and actions that might enable success in ultra-rare development without unintended consequences on existing traditional rare programs. The following page highlights key takeaways from the discussions.



Key Takeaways

To Fix a Problem, You Need to Define It

Despite the progress made in the past 40 years, only 5% of rare diseases have an FDA-approved drug. To ensure that all rare diseases, including ultra-rare diseases, have an equitable chance at an approved therapy, the obstacles that ultra-rare populations face need to be clearly defined and addressed with targeted solutions.

Innovative Trial Designs Needed

Due to the challenges posed by low prevalence and variable disease progression in ultra-rare diseases, traditional clinical trial designs aren't feasible. Innovative approaches, including the use of surrogate endpoints and allowing patients to be their own controls, are essential. Enhancing data sharing among stakeholders may improve clinical trial design and outcomes for ultra-rare diseases.

Ethical Considerations in Trials

Placebo arms may be unethical for high-mortality conditions, particularly in pediatric populations. Alternatives like natural history studies and simulations are needed, understanding that they come with their own unique challenges.

Paradigm Shift in Risk Sharing

To enable greater successes in the development of ultra-rare therapies, there needs to be a benefit-risk recalibration across stakeholders and a refinement of sponsors' and regulators' shared tolerance for uncertainty. Regulatory guidance would help create a more balanced risk-sharing between regulators and sponsors and facilitate greater predictability and consistency in the flexibility that regulators apply.

Regulatory Flexibility and Concerns

Ultra-rare diseases are significantly limited in their ability to gather the evidence needed to meet agency standards for approval. While the FDA has successfully applied flexibility in evaluating evidence for ultra-rare therapies, there's concern that this flexibility isn't applied consistently. A regulatory framework specific to ultra-rare diseases could provide greater predictability and rebalance the risk paradigm. There must, however, be careful consideration in developing such a framework to ensure there aren't unintended consequences for other rare diseases.

Importance of Real-World Evidence

Where patient populations are exceptionally small and conventional randomized controlled trials may not be feasible, there may be a case for permitting regulators to weigh the totality of evidence in their decisions. This approach would allow for real-world evidence, including open label extension studies, natural history studies, and patient experience, to be considered rather than adhering strictly to traditional study requirements. Real-world evidence can complement clinical trial data and should be considered in regulatory evaluations.

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A regulatory framework specific to ultra-rare diseases could provide greater predictability and re-balance the risk paradigm.

I. Introduction and Background

Current State of Rare Therapy Development – Significant progress has been made, but ultra-rare disease populations are being left behind.

The prospect for success in rare disease therapy development has significantly improved in recent years, driven by scientific innovation, patient engagement, economic incentives, regulatory policy changes, and collaborative efforts among stakeholders.

Much of this change would not have been possible without the Orphan Drug Act (ODA) of 1983. This landmark legislation incentivized pharmaceutical companies to invest in research and development (R&D) for treatments for rare diseases, defined as those affecting fewer than 200,000 people in the U.S. population. Key provisions included tax credits and grant funding for research, seven years of market exclusivity for FDA-approved orphan drugs, fee waivers, and FDA assistance to encourage faster and cheaper approval processes. Thus, in addition to catalyzing and sustaining the industry investment needed to create what is now a robust ecosystem of orphan disease drug developers, the ODA also provided rare diseases with the national recognition needed to drive change on a larger scale.

Yet, for many of these diseases, making an economic case for the extraordinary investment and financial risk of R&D is only the beginning. The journey from candidate to market is profoundly complex for rare diseases. Small patient populations, limited clinical data, phenotypic heterogeneity, diagnostic delays, high morbidity, and pediatric-onset all make it exceptionally challenging to apply the same strategies and meet the same standards for demonstrating safety and efficacy as the FDA traditionally applies. While the FDA has the authority to exercise its scientific judgment in determining the kind and quantity of data a sponsor may provide to meet the statutory standard of "substantial evidence" from "adequate and well-controlled studies," a number of policy changes over the years have helped streamline the regulatory process, particularly for therapies for life-threatening diseases with unmet medical needs, such as rare diseases.

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In 1997, Congress enacted the Food and Drug Administration Modernization Act (FDAMA), which authorized the FDA to approve drugs based on a single adequate and well-controlled clinical trial accompanied by confirmatory evidence rather than the traditional requirement of two such trials. This change aimed to expedite the approval process, especially for therapies addressing serious or life-threatening conditions with unmet medical needs. The following year, the FDA issued guidance detailing how this standard could be met, specifying that confirmatory evidence might include data from related clinical trials, studies demonstrating a strong mechanistic understanding, or compelling preclinical data.

Recognizing the challenges of conducting lengthy clinical trials to reach definitive clinical endpoints, particularly for patients with serious conditions, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012. This legislation expanded the FDA's authority to use surrogate or intermediate clinical endpoints in accelerated approval processes, allowing for earlier evaluation of a therapy's safety and efficacy. Concurrently, the FDA began integrating Patient-Focused Drug Development (PFDD) principles into its regulatory framework. This initiative emphasizes incorporating patient perspectives into drug development and regulatory decision-making, ensuring that therapies align with patient needs and preferences. Subsequently, the FDA established several programs and issued guidances to facilitate the inclusion of patient input in assessing the risk-benefit profiles of new therapies.

To further support the rare disease community, the FDA has also developed specialized programs and resources, including:

- **FDA Rare Disease Innovation Hub**: Established in November 2024, the hub will serve as a central resource for coordinating efforts to promote innovation in rare disease therapies and offer support and information to stakeholders.
- **CDER Accelerating Rare Disease Cures (ARC) Program**: Launched in May 2022, the program seeks to address the unique challenges inherent in rare disease drug development by fostering scientific and regulatory innovation and enhancing stakeholder engagement.
- **Leader 3D Public Report**: Through interviews and feedback, this report identifies challenges in rare disease product development and outlines strategies for progress through education and public outreach.
- **Genetic and Metabolic Diseases Advisory Committee (GeMDAC)**: This committee provides expert advice on rare genetic and metabolic diseases, guiding regulatory decisions and policy development.
- **Rare Disease Endpoint Advancement (RDEA) Pilot Program**: Established in October 2022, the program seeks to address the unique challenges in rare disease drug development by providing sponsors with early and ongoing engagement with the FDA to discuss and refine innovative endpoint strategies.
- **Split Real Time Application Review (STAR) Pilot Program**: Established to allow patients earlier access to therapies that address unmet medical needs by shortening the time from submission to the action date.
- **Center for Clinical Trials Innovation (C3TI)**: While not exclusive to rare diseases, C3TI aims to enhance the efficiency and effectiveness of clinical trials across various therapeutic areas.

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The impact of these economic incentives, policies, and regulatory programs is apparent in the number of orphan drug approvals realized in the past four decades. Prior to 1983, it is estimated that fewer than 38 orphan drugs had received FDA approval.[1] Since then, over 7,000 orphan drug designations have been granted, resulting in FDA approval of over 1,100 therapies.[1,2] While this progress should be celebrated, the reality is that the majority of these therapies never achieve FDA approval, and of those that do, a large percentage treat a small minority of rare diseases.

A 2022 analysis of FDA-approved orphan drugs revealed that the 1,122 FDA-approved orphan drugs available at the time provided therapies for 392 rare diseases, which accounted for less than 5% of all known rare diseases.[3] Further, 38% of these FDA-approved orphan drugs were indicated for rare cancers, including 19 therapies for multiple myeloma, a blood cancer that impacts an estimated 179,063 Americans.[3,4] Oncology products also make up the majority of accelerated approval therapies (67%), having leveraged the reuse of surrogate endpoints in clinical trials across conditions in different conditions.[5]

Given that approximately 84.5% of the 10,000 known rare diseases have a point prevalence of less than 1 in 1,000,000, and in addition, an average of 300 new rare genetic diseases are identified each year, it's clear that there is much more work to be done to improve outcomes for those diseases with very small patient populations.[1,6]

With all that has been done to support rare therapy development, this begs the question – do very small patient populations need a different set of resources and regulatory changes to ensure more equitable outcomes and successes in therapy development? If that is the case, will there be a need to take such proposals for a formal characterization or definition of "ultra-rare" similar to what was required for the Orphan Drug Act to generate momentum and define who and what is eligible and what unintended consequences could result from such efforts?

[1]Rare Coalition. ODA Overview. Rare Coalition, n.d., https://www.rarecoalition.com/wp-content/uploads/ODA-Overview.pdf.

[2]U.S. Food and Drug Administration. Orphan Drug Designations and Approvals. U.S. Department of Health and Human Services, n.d., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm.

[3]National Cancer Institute. Cancer Stat Facts: Multiple Myeloma. Surveillance, Epidemiology, and End Results (SEER) Program, n.d., https://seer.cancer.gov/statfacts/html/mulmy.html.

[4]Fermaglich, Lewis J, and Kathleen L Miller. "A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act." Orphanet journal of rare diseases vol. 18,1 163. 23 Jun. 2023, doi:10.1186/s13023-023-02790-7

[5]Domike, R., Raju, G.K., Sullivan, J. et al. Expediting treatments in the 21st century: orphan drugs and accelerated approvals. Orphanet J Rare Dis 19, 418 (2024). https://doi.org/10.1186/s13023-024-03398-1

[6]Nadeau, K.C., et al. "A Call to Arms against Ultra-Rare Diseases." Nature Biotechnology, vol. 39, no. 4, 2021, pp. 401–407.

In May 2024, recognizing the need for a forum, the EveryLife Foundation convened a workshop of experts from the patient community, industry, and regulatory agencies to discuss the considerations and implications of establishing a statutory definition for ultra-rare diseases and the metrics that would generate an evidence-based definition should one be recommended. This paper describes many of the themes that emerged, including key considerations that should be taken into account in establishing a definition of ultra-rare and potential policy solutions.

II. Key Considerations for Establishing a Statutory Definition of Ultra-Rare

Ultra-rare should be characterized by more than population size and in a way that can be operationalized.

The workshop began with a review of results from a pre-workshop survey on the need for a formal definition of "ultra-rare" and what characteristics should inform a definition if one were to be created. At the outset of the workshop, the majority (60%) of respondents voiced support for defining ultra-rare diseases, with only 4% responding "no" and 35% responding "unsure". This same poll was repeated at the end of the day, with 74% voicing support for establishing a formal definition and 22% unsure, demonstrating that workshop discussions affirmed this position. When asked what characteristics should inform a potential definition, 20% said the number of patients, followed by 15% of respondents indicating that both disease severity and clinical trial feasibility, indicating a solely numerical definition may not be the best approach to characterizing ultra-rare diseases.

Throughout the workshop, presenters and panelists shared compelling arguments for the need for additional support for ultra-rare disease, but many stopped short of recommending specific criteria or a numerical cutoff point distinguishing rare from ultra-rare. Concerns were raised that focusing on prevalence alone could unintentionally create inequities by excluding traditional rare conditions that face similar barriers, particularly those with diagnostic hurdles or less advocacy representation. It was also noted that some diseases might fluctuate in their prevalence over time. Setting a specific threshold could inadvertently exclude conditions on the borderline, leading to disparities in support and funding.

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Many called for a more nuanced definition that is reflective of the barriers that ultra-rare disease populations face navigating the long and unpredictable journey from drug discovery to market access. Among those, clinical trial design, access to care and clinical trials, ethical obligations, and regulatory opportunities emerged as primary themes. The following are considerations that should be taken into account when developing a definition of and policies for "ultra-rare" diseases.

Clinical Trial Design

Due to the low prevalence of ultra-rare diseases and exclusion criteria that further narrow the eligible population, it is often not feasible or ethical to execute a well-controlled, placebo-matched, and adequately powered study. Thus, evaluating potential therapies for ultra-rare disease populations frequently requires innovative clinical trial designs coupled with regulatory flexibility.

Additionally, for many ultra-rare diseases, the disease progression may be variable, or there may not be enough data to stage the disease reliably or predict its progression. These factors make it challenging for drug developers to design clinical trials that can effectively capture significant results and control for patient-to-patient variability. Where known natural histories are poorly understood, or the disease progression is variable, allowing patients to be their own controls

can be a powerful approach, but there should be greater clarity on when such approaches are more appropriate than more traditional trial design approaches.

Surrogate endpoints can be effective for reducing study length and demonstrating efficacy but the pathway for qualifying surrogate endpoints for rare diseases is unclear. The FDA determines the acceptability of these measures on a case-by-case basis, considering such factors as the disease, the patient population being studied, therapeutic mechanism of action, and availability of treatments.[7] For medicines approved through the Accelerated Approval Pathway, at a minimum, there must be "credible evidence" suggesting the surrogate endpoint's potential to predict clinical benefit. However, for many rare diseases, small patient populations, and genotypic and phenotypic heterogeneity make selecting and qualifying an endpoint that is both meaningful to patients and sensitive to change a significant challenge. This creates difficulty in designing trials that meet traditional evidentiary standards. To advance the acceptance of surrogate endpoints, there must be a continued commitment to improving the qualification process for those endpoints that reflect patient experiences and values.[8]

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CASE STUDY

Case Study – Successful Ultra-Rare Therapy Development – Activated PI3K Delta Syndrome, Joenja Example

- Activated PI3K Delta Syndrome is an ultra-rare primary immunodeficiency caused by genetic mutations in the PIK3CD gene, which impacts the normal development and function of white blood cells, that is highly heterogenous with an estimated prevalence of 1-2 affected people per million.
- In 2015, Novartis began a 2-part Phase 2/3 multi-center clinical trial that took over six years to complete. Part 1 of the study was a 12-week non-randomized open-label, within-patient dosage study (n=6).[9]
- Part 2 of the study was a 12-week blinded, randomized, placebo-controlled study of 31 adult and pediatric patients 12 years of age and older with confirmed APDS-associated genetic PI3Kδ mutation, with a documented variant in either PIK3CD or PIK3R1.[10]
- The co-primary efficacy endpoints were improvement in lymphoproliferation (or reduction in the size of lymph nodes) and the normalization of immunophenotype as measured by the percentage of naïve B cells out of total B cells. By day 85 of the study, patients taking Joenja saw a reduction in lymph node size and a 37 percent improvement in naïve B cells counts compared to placebo, indicating a correction of the underlying immune defect.[11]
- In 2019, Pharming licensed Joenja from Novartis in a $20 million agreement, with milestones and royalties including the rights to purchase the anticipated Pediatric Rare Disease Priority Review Voucher for a pre-agreed percentage of the PRV value ($21 million).[12]
- Joenja was approved in March 2023, with market access beginning in April of 2023, for the treatment of the ultra-rare disease-activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS). The first approval for this indication in the US.[13]
- Upon licensing the asset from Novartis, Pharming's CEO Sijmen de Vries noted that the drug was expected to be "a perfect strategic fit for [Pharming's] existing medical and commercial infrastructure."

[7]U.S. Food and Drug Administration. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. U.S. Department of Health and Human Services, 20 Sept. 2023, https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure.

[8]U.S. Food and Drug Administration. Qualification Process for Drug Development Tools: Guidance for Industry and FDA Staff. U.S. Department of Health and Human Services, 13 Jan. 2023, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-process-drug-development-tools-guidance-industry-and-fda-staff.

[9]National Institutes of Health. (2022, August 10). Study of Efficacy of CDZ173 in Patients With APDS/PASLI. Clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02435173?intr=Leniolisib&rank=5

[10]Ibid

[11]Center for Drug Evaluation and Research. (2023, March 24). FDA approves first treatment for APDS. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-activated-phosphoinositide-3-kinase-delta-syndrome

[12]Manalac, T. (2023, March 27). Pharming's Leniolisib gains FDA approval in ultra-rare disease. BioSpace. https://www.biospace.com/pharming-s-leniolisib-gains-fda-approval-in-ultra-rare-disease

[13]Center for Drug Evaluation and Research. (2023, March 24). FDA approves first treatment for APDS. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-activated-phosphoinositide-3-kinase-delta-syndrome

Placebo arms may not be possible or ethical, particularly for diseases with a high mortality rate or those that affect pediatric patients. Natural history studies and simulation approaches may help to fill this gap, but both evolving approaches have their challenges and limitations. There may be opportunities to leverage artificial intelligence and Bayesian statistics to simulate control arms and address challenges with small, heterogeneous patient populations. However, further research on these approaches is needed to better understand how they can be applied and their limitations.

Finally, publishing cross-agency consensus on best practices for tackling these challenges is essential for achieving greater predictability and transparency. While the FDA has programs currently focused on these very issues, to be effective, coordination and communication between these efforts, as well as with the rare disease community, is imperative.

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CASE STUDY

Successful Ultra-Rare Therapy Development – The SOD1 Genetic Variant Amyotrophic Lateral Sclerosis (ALS), Tofersen Example

- SOD1 variants are linked to a subset of ALS cases, leading to the production of misfolded SOD1 proteins that contribute to motor neuron degeneration. Approximately 600 individuals (2% of total ALS cases) have SOD1-mediated ALS.
- Tofersen is an antisense oligonucleotide designed to bind to SOD1 mRNA and reduce the synthesis and accumulation of SOD1 protein.
- A Phase 3 trial was used to evaluate Tofersen's efficacy and safety in adults with ALS associated with a mutation in the SOD1 gene (SOD1-ALS).
- In this pivotal trial, the primary endpoint (change in ALS Functional Rating Scale-Revised (ALSFRS-R) score from baseline to 28 weeks) did not reach statistical significance; however, prespecified secondary analyses showed tofersen-associated evidence of target engagement (reduced SOD1 protein levels) and a subsequent potential slowing of neurodegeneration evidenced by reductions in neurofilament light chain (NfL) levels.
- Given challenges of clinical endpoint measurement in ALS due to high variability in disease progression across individuals living with the disease, which can be particularly challenging in a short (6-month) study duration, tofersen-associated NfL reductions that preceded clinical benefit served as critical evidence of the potential for treatment efficacy.
- NfL is a well-established marker of axonal injury and neurodegeneration with higher baseline levels known to be associated with faster disease progression and shorter survival in ALS.
- The tofersen-associated reduction in NfL in VALOR was viewed as a potential indicator of reduced axonal injury and neurodegeneration, which is a hallmark of ALS pathophysiology.
- In April 2023, tofersen received Accelerated Approval (AA) from the FDA based results from VALOR and its open label extension (OLE) based on the surrogate biomarker endpoint (NfL), and clinical benefit still has to be established.
- The FDA also allowed Biogen to extend the duration of the study beyond its initial 6-month duration as it was realized that NfL levels would only show discernable clinical benefit after 28 weeks. This realization emphasized the need for extended follow-up periods in trials using biomarkers like NfL to correlate with longer-term outcomes.

[14]Appel SH, Thonhoff JR. Barriers to Tofersen Therapy for Variant SOD1-Mediated ALS. JAMA Neurol. Published online October 07, 2024. doi:10.1001/jamaneurol.2024.3331

CASE STUDY

Challenges in Ultra-Rare Therapy Development: The Barth Syndrome, Elamipretide Example

- Barth syndrome is an ultra-rare, life-threatening disease characterized by multiple clinical manifestations, including cardiomyopathy, skeletal myopathy, neutropenia, and growth delays. There are fewer than 300 known cases globally, with fewer than 150 in the U.S.
- In a 2017 trial for elamipretide, only 106 individuals with Barth Syndrome were identified in the U.S. Age restrictions and other criteria reduced the eligible pool to 55, and only 12 consented to participate, representing over 20% of the known eligible U.S. patient population.
- The FDA and sponsors debated whether it was even ethical to conduct a placebo-controlled trial due to statistical powering constraints in such a small patient population.
- The Phase 2 trial was short (three months) and used a double-blind, placebo-controlled crossover design followed by an open-label extension. Given the small patient population, a contemporaneous natural history control cohort was utilized to establish a control for the open-label data. This dataset included 19 patients and provided a comparative framework alongside the interventional trial data, over 50% of the eligible US population.
- Surrogate markers, including physiological endpoints like heart function and a disease-specific biomarker, the MLCL:CL ratio,, were pivotal in making the case for efficacy, alongside functional measures like the 6-minute walk test (6MWT) and patient-reported outcomes.
- Signals of efficacy were observed during open-label extension and as compared to the natural history control. Regulatory challenges included educating regarding the indication, mechanism of disease and natural history of disease, the small trial size, lack of a concurrent placebo-control for the data, and statistical limitations intrinsic to a natural history control study.
- Over eight years, elamipretide has been through four different divisions of the FDA that have assessed endpoints and trial designs differently.
- In October 2024, the Cardiovascular and Renal Drugs Advisory Committee held a meeting to discuss the use of elamipretide to treat Barth syndrome. The committee voted 10-6 in favor of the efficacy of elamipretide for the treatment of Barth syndrome. The FDA is expected to make a decision in January 2025.

Access to Clinical Trials and Treatments and Ethical Obligations

Any definition of ultra-rare and related policies take into account the consequences they might have, both direct and indirect, on access to clinical trials and therapies post-approval.

Disease severity and heterogeneity can make it difficult to enroll participants and minimize variability in clinical trial participants. For example, ultra-rare diseases disproportionally affect pediatric patients and have a high mortality rate as well as a significant morbidity impact. For ultra-rare degenerative diseases, it can be difficult to confirm the diagnosis in the early stages before the disease has caused significant impairment, which ultimately excludes many patients from being eligible for clinical trials. In some ultra-rare diseases, it may be impossible to conduct a second trial, should one be necessary, due to the entire eligible population having already participated in the initial effort.

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Additionally, because clinical trials for ultra-rare diseases often cannot meet the same study statistical power requirements as regulators apply to clinical trials for more common diseases, there is concern that the flexibility afforded to regulators to assess the available and often atypical evidence presented for ultra-rare disease treatments may erode payer confidence in the rigor of regulators' decisions and the value proposition of the treatment. Stakeholders recognize this dynamic and the need to demonstrate that these flexibilities are necessary to overcome the realities of rare diseases and do not imply a lower benefit-risk standard.

The incentives established by the Orphan Drug Act, including a 25% tax credit on applicable research and development costs (reduced from a prior level of 50% and at times targeted for further reduction), waived FDA user fees for new compound submissions, and the potential for seven years of marketing exclusivity for approved treatments, have helped induce greater investment in orphan drug development, given the small population sizes. However, very small patient populations mean that there is a smaller market from which to recoup costs, though workshop participants cautioned against efforts to establish differential economic incentives for ultra-rare diseases due to the risk of eroding overall rare disease incentives. Accordingly, the price of the medication, once approved, may be more than patients and healthcare plans can afford, effectively preventing small patient populations from accessing therapies.

Finally, it was recognized that drug developers, regulators, and patient advocates all have a moral obligation to ensure that any policies that incentivize the development of treatments for ultra-rare diseases encourage the development of effective therapies in a manner that is equitable to all members of the rare disease community. Before establishing a definition for ultra-rare, there should be consideration of whether the policies, incentives, or flexibilities such as the definition would be used to operationalize might be a detriment to the development of treatments for other rare diseases.

There is currently no regulatory pathway specific to ultra-rare therapies.

Regulatory Opportunities

There is a lack of regulatory precedent for ultra-rare diseases, making it challenging to navigate the approval process. While the FDA has exercised flexibility in determining the type and amount of evidence for rare disease therapies, in some cases leading to successful approvals, the lack of clarity and consistency in decision-making prevents sponsors from gauging the likelihood of success.

There also needs to be a shift in the risk-sharing paradigm between regulators, sponsors, and investors in ultra-rare therapies. The lack of regulatory precedent shifts risks heavily towards sponsors and investors, which already shoulder significant risk due to the limited commercial potential of many ultra-rare disease therapies. With substantial unmet need, there needs to be a more balanced sharing of risks between regulators, sponsors, and investors, as well as the development of potential new incentives to developers.

To that end, while the FDA has developed several programs and resources to support developers of therapies for ultra-rare diseases, there is currently no regulatory pathway specific to ultra-rare therapies. Due to the challenges of conducting well-controlled and adequately powered clinical trials for ultra-rare populations, a panelist suggested that a regulatory pathway specific to ultra-rare diseases could be established. For this pathway, it might be advantageous to allow regulatory agencies to consider the totality of evidence, including real-world evidence as well as conventional trials. Panelists and attendees disagreed whether a new pathway was required, with some arguing that the FDA has the statutory authority to consider the totality of the evidence, but requires a stronger framework from which to operationalize decision making in a more consistent way.

III. Potential Policy Solutions and Recommendations for the Future

In conclusion, workshop discussions confirmed that establishing an operational definition for ultra-rare diseases is not merely a matter of semantics but a critical step in addressing the unique challenges faced by patients, researchers, and healthcare systems in diagnosing, treating, and supporting those impacted by these exceptionally uncommon conditions.

A major challenge many ultra-rare diseases face is meeting the FDA's current standards for regulatory approval. While regulatory flexibility in decision-making has delivered some successes, there are challenges in applying that flexibility equitably. A new regulatory framework specific to ultra-rare diseases may reduce risk for developers while maintaining rigorous standards for regulators. For such a regulatory framework, it will be essential that innovative solutions are embraced, such as establishing conditions under which regulators can consider innovative trial designs and the totality of evidence, including real-world evidence. Refining pathways and establishing conditions under which regulators can consider the totality of the evidence — not just the data included in pivotal Phase 2 or Phase 3 studies - may provide valuable evidence for assessing the benefits and risks of treatments. In the case of ultra-rare diseases, real-world evidence might provide valuable and, in some cases, more persuasive evidence than controlled clinical trial results.

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However, it is also appreciated that developing such a framework will require drawing on learnings from past successes and failures as well as seeking input from regulators, sponsors, academics, care providers, and patients. Sharing these learnings with all stakeholders will enable greater predictability. To that end, it was suggested that programs enabling and incentivizing data sharing across sponsors and regulators could help de-risk drug development for ultra-rare diseases by allowing sponsors to learn from previous similar approaches, including both successes and failures, and identify trends that help improve the clinical trial design. These learnings should also be disseminated across the agency and developers to ensure that there is consistency in how they are applied and assessed.

A new regulatory framework specific to ultra-rare diseases may reduce risk for developers while maintaining rigorous standards for regulators.

Finally, the discussions underscored the importance of increased communication and coordination both across and between agencies, applicants, and patients. Some agencies have already recognized this need, including the FDA, which recently established the FDA Rare Disease Innovation Hub to serve as a single point of connection across FDA centers and divisions to enhance inter-center collaboration related to scientific, clinical, and policy issues and to establish workstreams to tackle related challenges, such as the consideration of novel endpoints, biomarker development and assays, innovative trial design, real-world evidence, and statistical methods. However, these programs are in their infancy, and there is a recognized need to ensure there is a greater awareness of these programs across and between agencies to ensure consistency. The following actions and next steps are recommended.

RECOMMENDATIONS FOR FUTURE ACTIONS

Develop Specific Regulatory Guidance for Ultra-Rare Therapies

- Establish guidance that promotes consistency in the development and approval processes for ultra-rare therapies while preserving existing incentives for rare diseases. To achieve this consistency, FDA will need to be clear on what evidence it will consider and how it will be evaluated. FDA will also need to ensure there is consistency in how these guidances are applied across the agency.
- Greater consistency in the development and approval process for ultra-rare therapies will also enable greater risk-sharing between regulators and sponsors.
- Ensure the FDA retains its ability to use scientific judgment in making risk-benefit decisions while providing clearer guidelines that facilitate benefit-risk deliberations between regulators and sponsors.
- Ultra-rare therapies need to be evaluated on the totality of evidence. Guidance could be used to outline the criteria under which regulators can consider the totality of the evidence, such as real-world data, including or beyond traditional pivotal studies.
- Clarify the appropriateness of alternative approaches to placebo controls, such as natural history studies, simulation studies (Model-Informed Drug Development), and crossover designs.
- Create expedited pathways for the qualification of surrogate endpoints and enhance harmonization across regulatory bodies.

Encourage Data and Knowledge Sharing Across Sponsors and Agencies

- Foster data-sharing initiatives that will enable sponsors, regulators, investigators, providers, and patients to learn from both successful and unsuccessful trial methodologies, especially alternative approaches.
- Implement a program that incentivizes sponsors to contribute data to a centralized data repository, facilitating consistency and improved outcomes.
- Ensure the outcomes of these initiatives are transparent to patients, who in many cases drive, fund, and participate in the technical aspect of research and drug development programs.

Enhance Inter-Agency Communication and Collaboration

- Promote stronger communication and sharing of insights among regulatory agencies to align on best practices and strategies for addressing ultra-rare therapies.
- An Inter-Agency Coordinating Committee, as called for in the FY2025 Labor, Health, and Human Services Appropriations Report, would facilitate this communication.

In summary, this workshop served as a critical springboard for bringing together regulators, developers, investigators, advocacy groups, and patients to collectively address the challenges of ultra-rare therapeutic development. The points outlined in the preceding Actions section should be viewed as a potential roadmap to continue the collective efforts of all rare and ultra-rare stakeholders in improving innovation ventures and, ultimately, rare care.

EVERYLIFE FOUNDATION FOR RARE DISEASES

About the EveryLife Foundation

The EveryLife Foundation for Rare Diseases is a 501(c)(3) nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments and cures. We do not speak for patients. We provide the training, education, resources and opportunities to make their voices heard. By activating the patient advocate, we can change public policy and save lives.
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