October 1, 2025

U.S. Food and Drug Administration
Dockets Management Staff (HFA-305)
Fishers Lane, Rm. 1061
Rockville, MD 20852
Sent via electronic delivery
Re: FDA-2025-N-1559 – Rare Disease Innovation, Science, and Exploration Public Workshop Series

To Whom It May Concern,

Please accept our proposal for a Rare Disease Innovation, Science, and Exploration (RISE) Workshop **Using Primary Disease Biomarkers to Address Low-Prevalence Neurodegenerative Diseases with Single Gene Defects**

We include a detailed outline as requested by the agency below:

—a description of the proposed topic;

The development and regulatory evaluation of therapies for neurodegenerative lysosomal diseases (nLDs) remains profoundly constrained by the intersection of extreme rarity, phenotypic heterogeneity, and rapid disease progression, creating one of the most pressing unmet needs in rare disease drug development. This challenge reflects a broader pathophysiological paradigm shared across many rare metabolic diseases driven by monogenic enzymatic defects and substrate accumulation, the vast majority of which still lack approved therapies. Classification of primary disease biomarkers could support an accelerated pathway where standard trial methodologies are often unfeasible. The rarity, phenotypic heterogeneity, and rapid disease progression in early-onset forms of nLDs present formidable barriers to traditional drug development and regulatory evaluation. Conventional trial methodologies are frequently infeasible due to extremely limited sample sizes, ethical barriers of placebo-controlled designs, and the lack of validated, disease-specific endpoints. These constraints underscore the urgent need for regulatory science innovation that supports both acceleration of therapeutic development and rigorous patient-centered approaches that reflect the lived experience and clinical priorities of affected individuals and families.

—suggested speakers and/or subject matter experts;

The complexity and urgency of advancing therapeutic development for nLDs necessitate engagement from a diverse set of subject matter experts (SMEs). Experts in the historical and technological evolution of nLD treatment including enzyme replacement, substrate reduction, gene therapy, and small molecule approaches will provide essential context for understanding the scientific and regulatory inflection points that have shaped the current landscape. We recommend:

- Panel discussions where biomarkers could be established as primary disease biomarkers (PDBs) including members from patient advocacy organizations, academic key opinion leaders, and representatives from industry. These panels will elucidate the direct experiences navigating the development, access, and approval of treatments for

nLDs and will ground the discussion in real-world impact, offering critical insights through case studies of successful and stalled therapeutic programs.

To foster a solution-oriented dialogue, SMEs in regulatory science, clinical trial methodology, digital health technologies, and patient-reported outcomes will lead discussions on persistent challenges in developing and evaluating therapies for rare neurodegenerative conditions with very small populations. We recommend:

- Discussion based on recently announced programs by FDA leadership, including proposals for pathway acceleration based on biologically plausible mechanisms and strong pathophysiologic rationale. The inclusion of regulatory experts and policy scholars will enable a balanced exploration of the potential for more adaptive, expedited regulatory pathways. These new and existing pathways can be best utilized in specific rare disease contexts.

Collectively, these expert perspectives will equip stakeholders with the scientific, clinical, regulatory, and ethical frameworks needed to chart a more efficient and patient-centered path forward for nLD therapy development.

—a description of the impact of the topic on the development and regulatory science of rare disease therapies;

Conditions such as GM1 gangliosidosis, GM2 (Tay-Sachs and Sandhoff diseases), Sanfilippo syndrome, Hunter syndrome, Krabbe disease, Batten disease, Niemann-Pick disease, and metachromatic leukodystrophy, share well-defined biochemical etiology that drive progressive substrate accumulation in neurons and glia, culminating in catastrophic neurodegeneration. Despite this clear pathophysiological mechanism, the identification of promising candidate biomarkers, and a rapidly expanding pipeline of gene therapy and substrate reduction approaches, very few therapies for nLDs have achieved FDA approval despite decades of intensive research efforts.

The traditional drug development paradigm, centered on randomized, placebo-controlled trials and conventional clinical outcome measures, is fundamentally misaligned for irreversibly progressive nLDs. Patient populations are exceedingly small, geographically dispersed, and phenotypically heterogeneous. Diagnostic delays further narrow eligibility, as most patients are identified only after symptom onset, rendering them no longer eligible for clinical trials restricted to pre-symptomatic or minimally affected individuals. While pre-symptomatic siblings represent a theoretically ideal study population, their scarcity makes enrollment logistically and financially prohibitive, and the timeline required for such studies is incompatible with the urgency of these diseases.

Individuals with nLDs and their families frequently participate in multiple natural history studies, often over several years, only to find that the resulting data sets are deemed inadequate for regulatory use. Concurrently, promising therapeutic candidates are abandoned due to trial infeasibility, lack of validated endpoints, and investor attrition following perceived regulatory or commercial failure. Clinical benefit is often apparent to families and clinicians. For example, patient reported outcomes (PROs) frequently capture improvements in swallowing, motor stability, or cognitive alertness, benefits that are often missed by traditional trial endpoints. Consequently, the observed “clinical benefits” are frequently inapplicable in populations with rapidly regressing neurodevelopment.

To address these systemic failures, we propose a regulatory science framework anchored in mechanism-based flexibility and PDBs, biological measures that reflect substrate burden, enzyme activity, and early therapeutic engagement. In nLDs, biomarkers such as CSF substrate levels, serum/CSF biomarker profiles, and neurofilament light chain (NfL) provide quantifiable, disease-relevant signals that can be used as intermediate endpoints for accelerated approval.

This perspective echoes recent commentary by Dr. Marty Makary and colleagues' advocacy for expedited regulatory pathways based on plausible mechanisms of action, particularly in single-enzyme disorders. With the pending publication in the New England Journal of Medicine, there will be a need to understand how the plausible mechanism pathway applies to primary disease biomarkers. Additionally, more discussion is needed on how the Rare Disease Evidence Principles could be applied to other disease-modifying treatments for clinically meaningful outcomes. In these contexts, gene therapy or enzyme replacement therapy that demonstrably corrects the underlying biochemical defect when coupled with validated delivery methods, target tissue engagement, and measurable changes in disease biomarkers, comprises sufficient evidence for conditional approval. Such an approach is especially compelling when no approved therapies exist, and the alternative is certain neurological decline and death.

Importantly, adopting this framework does not imply a relaxation of scientific standards. Rather, it demands a recalibration of regulatory expectations to match the scientific realities of nLDs. Safety and biomarker engagement can and should be measured with rigor; post-marketing surveillance can ensure longitudinal evaluation of benefit; and the moral imperative to act in the face of irreversible disease should no longer be dismissed due to inappropriate evidentiary thresholds.

The issues being faced amongst the nLDs are emblematic of both the promise of precision medicine and the peril of outdated regulatory norms. The tools to measure disease activity exist. The scientific rationale for intervention is strong. The diverse cadre of stakeholders, including patients, scientists, clinicians, and caregivers, is ready. What is urgently needed is a regulatory framework that recognizes the legitimacy of mechanism-driven drug development in rare, devastating, and time-critical conditions. Without such change, we will continue to lose both patients and therapeutic opportunities.

—the disease state(s) affected by the challenge highlighted in the submission;

Neurodegenerative lysosomal diseases (nLDs)

—if relevant, related FDA guidances or existing programs addressing the challenge highlighted in the submission;

Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Result From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies

Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics

Qualifying Biomarkers to Support Regulatory Pathways

nLDs present a unique and well-defined biological framework that is not adequately accommodated by conventional regulatory pathways. In these diseases, therapeutic targeting of

a known enzyme defect can yield measurable reductions in substrate accumulation and downstream pathology, offering a clear mechanism-based rationale for intervention. However, despite this pathophysiological clarity, developers face persistent barriers in providing traditional evidence of clinical effectiveness, particularly in the absence of short-term behavioral or survival outcomes. The FDA's guidance *"Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Result From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies"* (2023) directly acknowledges these challenges and affirms that flexibility in evidentiary standards, such as use of PDBs, substrate clearance data, or evidence of biochemical correction, may be appropriate in supporting efficacy for replacement or corrective therapies in these contexts. This is reinforced by the Accelerated Approval pathway under *"Expedited Programs for Serious Conditions – Drugs and Biologics"* (2014), which permits approval based on surrogate endpoints reasonably likely to predict clinical benefit.

Patient advocacy organizations that support this RISE proposal:

- Ara Parseghian Medical Research Fund
- B Brave Foundation
- BDSRA Foundation
- Beyond Batten Disease Foundation
- Blu Genes Foundation
- CATS Foundation
- Cure Dhdds
- Cure GM1 Foundation
- Cure Sanfilippo Foundation
- Cure Tay-Sachs Foundation (CTSF)
- Drew's Hope
- Firefly Fund
- ForeBatten Foundation
- Gaucher Community Alliance
- Helen's Pink Sky Foundation
- Krabbe Connect
- Lehrman Family Fund
- Mathew Forbes Romer Foundation
- Mila's Miracle Foundation
- MLD Foundation
- Muenzer MPS Research & Treatment Center
- National MPS Society
- National Niemann-Pick Disease Foundation (NNPDF)
- National Tay-Sachs & Allied Diseases Association (NTSAD)
- Noah's Hope - Hope4Bridget
- Our Promise to Nicholas Foundation
- Project Alive
- The Ryan Foundation
- Taylor's Tale
- Wylder Nation Foundation

Biotechs and academic groups:

- Azafaros

- BridgeBio
- Children's Hospital Colorado
- The Gelb Laboratory
- Gemma Biotherapeutics, Inc.
- JCR Pharmaceuticals Co., Ltd.
- Latus Bio
- LDRTC (Lysosomal and Rare Disorders Research and Treatment Center)
- Nationwide Children's Hospital
- Orphan Disease Accelerator
- Orphan Disease Center, University of Pennsylvania, Perelman School of Medicine
- Pyra Bio
- Religaire Bio LLC
- Rush University Medical Center
- Spur Therapeutics
- University of Rochester Batten Center