August 2, 2024

The Honorable Diana DeGette
2111 Rayburn House Office Building
Washington, DC 20515-0601

The Honorable Larry Bucshon, M.D.
2313 Rayburn House Office Building
Washington, DC 20515-1408

Dear Congresswoman DeGette and Congressman Bucshon:

On behalf of the EveryLife Foundation for Rare Diseases, an organization dedicated to empowering the rare disease patient community to advance laws and policies to improve lives of all people and families impacted by rare diseases and disorders, thank you for your dedication and leadership in furthering the achievements of the 21st Century Cures Act. Your commitment to enhancing a patient-centered healthcare system is instrumental in advancing research, improving treatment options, and supporting patients and families affected by rare diseases.

The passage of the 21st Century Cures Act was a significant milestone for the rare disease community and helped to reshape the development and therapeutic landscape. Its focus on provisions that advanced research into rare disease including authorizing and funding the *All of Us* Precision Medicine program, strengthening how the Food and Drug Administration (FDA) uses patient experience and patient-focused drug development data, and advancing innovative approaches to conducting clinical trials, innovations that are of particular importance when studies involve small populations of patients. As we get closer to the 10-year anniversary of 21st Century Cures, we believe it would be a most opportune time to commemorate progress achieved to date while pushing for continued advancements.

More than 30 million Americans live with one or more rare diseases. While these conditions individually affect smaller populations compared to common diseases, estimates suggest that one in every 10 Americans lives with a rare disease. Interest in developing therapies for rare diseases has grown significantly since the passage of the historic Orphan Drug Act forty years ago, resulting in over 1,200 approved indications for rare diseases, including recent breakthroughs in cell and gene therapy and CRISPR technologies. Despite these advancements, at least 95% of the over 10,000 known rare diseases still lack approved treatments.

Navigating the average 15+ year process to develop treatments for rare diseases presents numerous challenges. Even when a product successfully reaches approval, patients often encounter unnecessary delays and barriers to accessing these treatments. These delays lead to avoidable health deterioration and reduced quality of life for members of the rare disease community. The current regulatory systems struggle to effectively address the unique complexities inherent in rare diseases. With over 10,000 rare

diseases affecting more than 30 million Americans, the need for a streamlined and focused approach in regulatory science and review processes cannot be overstated.

On July 17, 2024, the FDA announced the establishment of a *Rare Disease Innovation Hub (the Hub)* to help address these regulatory challenges specific to rare diseases. Establishing such infrastructure fulfills a priority of the EveryLife Foundation and aligns with a key provision of your 2021 Cures 2.0 proposal. We commend the agency for its efforts and recognition of the unique needs of the patients we represent. Small patient populations create challenges that require broad FDA expertise, such as those needed for identifying the natural progression of disease, dispersing clinical trial sites, detecting clinically meaningful outcomes, and designing adaptive clinical trials. We believe the Hub will foster needed collaboration across FDA centers to expedite the development and evaluation of treatments for rare diseases and ensure a consistent approach to all such reviews regardless of a product's review division or center.

While we are encouraged to see the establishment of the FDA Rare Disease Innovation Hub, there are several additional critical items a Cures package could support, including:

- **Requiring transparent reporting on current existing regulatory authorities, particularly as used for rare diseases.** The rare disease community has long been focused on enhancing the predictability and consistency of FDA's use of their regulatory flexibilities granted by Congress. To address these concerns and enhance the FDA's knowledge management capabilities, we recommend including within Cures 2.0 a provision that requires the FDA to report how it uses these flexibilities, particularly for rare disease treatments. This reporting would improve transparency, standardize reviewer training, and bolster stakeholder engagement by clarifying how the FDA applies its authorities and flexibilities. It would also build upon a provision in the 21st Century Cures Act that requires FDA to report on how it uses patient experience data as part of any approved drug application.

- **Ensure patient experience data is fully reflected as part of FDA's benefit-risk regulatory framework.** Although 21st Century Cures enables the FDA to evaluate the benefits and risks of potential therapies and gather patient perspectives, there is no requirement to include patient experience or patient-focused drug development (PFDD) data in its risk-benefit framework. To address this gap, we recommend including language from the Better Empowerment Now to Enhance Framework and Improve Treatments (BENEFIT) Act that ensures patient experience data—whether developed by a product sponsor, a patient advocacy organization, or an academic institution—is considered in the risk-benefit assessment. This addition would signal to all stakeholders that patient experience and PFDD data will be fully integrated into the review process and encourage the development of scientifically rigorous and meaningful tools and data.

- **Build on the significant progress made by the Patient Focused Drug Development movement.** 21st Century Cures Act and subsequent PDUFA Reauthorizations have shifted the landscape for patient focused drug development. Through initiatives like patient focused drug development

meetings, the FDA benefit Risk Framework, increased opportunities for meaningful participation in advisory committees and the creation of the PFDD Guidance series, there is a deepened engagement and understanding of the patient perspective reflected in therapy development and evaluation decisions. While we celebrate this progress, we recognize the need for evolving and growing our commitments to incorporating all perspectives into regulatory considerations for rare disease products. As you consider an updated Cures 2.0 package, we encourage you to engage with rare disease stakeholders to better understand how the PFDD movement can evolve to ensure meaningful opportunities to engage with the FDA across multiple time points as patient community perspectives change and as the scientific landscape progresses.

- **Establish a Mechanism for Pre-Competitive Science-Focused Drug Development Conversations:** An emerging idea to build on the evolution of PFDD is the creation of a formal mechanism to convene FDA, patient, scientific and clinical experts and developers in the pre-competitive environment to systematically discuss drug development considerations in a particular rare disease. A meeting of this nature would facilitate the sharing of the latest in our understandings of a disease, allow for conversations about study design and endpoint considerations at a disease level rather than individual product considerations and enable more predictable and consistent agreement on regulatory approaches for that disease.

- **Establish an FDA Rare Diseases and Conditions Advisory Committee.** Despite the prevalence of rare diseases and disorders and the many uniquities associated with developing therapies to treat such conditions, the FDA has no current standing advisory committee on this topic. We appreciate the FDA's recent formation of a Genetic and Metabolic Diseases Advisory Committee to provide advice and recommendations on technical, scientific and policy issues related to medical products for genetic metabolic diseases. The new committee will add to the agency's ability to gain input from external experts on an important, but still specific segment of rare disease products. However, we believe a rare disease advisory committee can provide counsel to FDA on issues of importance across rare diseases such as emerging scientific and regulatory science topics. Such a committee can also be convened jointly, as needed, with a human drug or device committee for the purposes of advising on a candidate therapy but would not itself be tasked with advising on product evaluations. Existing advisory committees of this nature include the Pediatric, Patient Engagement, and Risk Communication committees.

- **Enhance FDA's Focus on Very Small Population Challenges.** In May of 2024, rare disease experts, patient communities, regulators and industry came together to discuss the needs and opportunities in very small, rare diseases, often referred to as ultra-rare diseases. While a full publication detailing the discussions and recommendations resulting from this convening is pending, the day's discussions underscored that additional policy solutions and regulatory efforts are needed to address regulatory science and public policy challenges to the development of treatments for very small populations. An updated Cures 2.0 package should include policies that enhance FDA's ability to dedicate efforts focused on innovative trial designs, regulatory flexibilities and manufacturing needs in ultra-rare populations.

- **Ensure Policy Adequately Supports the Translation of Scientific Advances to Novel Therapies.** The rare disease community observed the 40th anniversary of the passage of the Orphan Drug Act (ODA) in 2023, landmark legislation that reshaped the rare disease drug development landscape. The ODA provided therapy development incentives that have led to more than 1,200 orphan-designed approvals to treat rare diseases and disorders[1]. While the ODA was unquestionably a success, critical work remains. While we celebrate the innovation and collaboration that led to the approvals for the 5 percent with approved therapies, it must be understood that those communities have not yet been relieved of many of the most devastating or life-altering impacts of their diagnosis. Additionally, small, or ultra-rare, disease populations face increasingly significant challenges in the development of new therapies, including trial design, regulatory requirements, funding constraints, and extraordinary research hurdles due to their low prevalence numbers.

  An updated Cures package must recognize these challenges and support policies that will maintain Congress' longstanding recognition of and commitment to policies that incentivize rare disease research and therapy development to ensure that the remarkable advances in our understanding of rare diseases can be translated into new therapies and better health, regardless of the number of people affected by a given disease. One such policy, supported by 170 patient organizations, prioritizes two technical changes to the Inflation Reduction Act's orphan drug exemption that would support efficient rare disease innovation while not changing the number of approved indications a product can have before becoming eligible for Medicare negotiations.

- **Opportunities for earlier payer engagement**
  The rare disease community supports the codification of opportunities for engagement with stakeholders within the access ecosystem earlier in the approval process. This communication can help to better ensure that the measures being collected for inclusion within clinical trials and regulatory review will also be feasible for collection within the post-market environment. Only recently have patient communities begun to apply a remarkable level of engagement to the access environment; engagement that often begins when patients learn that long-awaited FDA approved products have launched into unfavorable access environments. For patients, these access barriers and delays translate into irreversible disease progression and – in some instances – pediatric patients are aging beyond the labeling requirements before life-saving access is granted. Potentially transformative new therapies, such as gene and cell therapies, promise life-altering improvements in patient health. But these innovative therapies have also presented complex new challenges for payers, and for patients and their families related to coverage decisions. These challenges represent the need for opportunities for earlier and innovative engagement within the therapeutic development process. The creation of a formal, early and voluntary program to facilitate interactions between payors and manufacturers would

[1] https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm

facilitate some elements of the desired engagement, leading to coverage and payment policies that facilitate patient access to novel therapies.

- **Ensure clinical trial inclusion criteria do not serve as an access barrier to patients for whom regulators have deemed the therapy to be scientifically and clinically appropriate.** FDA-approved prescribing-inserts are critically important because they inform patient, provider and payer decision making and – ultimately – access or lack thereof. However, our rare disease community is seeing a growing body of examples in which access is being narrowed further, particularly by payers substituting their own authority for that of the FDA by utilizing entry criteria from clinical trial inclusion criteria to serve as authorization criteria. This translates to patients denied access to innovative disease-modifying and potentially life-saving therapies even when they clearly fit within the population for whom the FDA approved. Importantly, rare disease drug development presents unique challenges due to small patient populations and heterogeneity of disease. This necessitates studying a more narrow, homogenous cohort in clinical trials to assess a treatment effect. The FDA evaluates the totality of evidence supporting the approval of a therapy and determines the eligible population included in the 'Indication and Usage' section of the FDA-approved label. While in some cases, the 'Indication and Usage' population could theoretically match the narrow group included in the clinical trial, in most cases, the FDA approves a drug that more closely reflects the real-world population likely to benefit from the therapy.

- **Uphold the FDA's statutory authority by forbidding public and private payers from making coverage policies based on the pathway that was used to obtain FDA approval.** Unfortunately, many self-funded insurance plans categorize drugs approved through the FDA's accelerated approval pathway as "experimental or investigational" in issuing negative coverage determinations. Therapies approved under the accelerated approval pathway are no longer experimental, having been evaluated via the same rigorous standard of safety and efficacy as products assessed via the traditional approval pathway. The distinction is in the type of endpoint evaluated for safety and efficacy. The accelerated approval pathway is predicated on an evaluation of efficacy based on a surrogate endpoint that is reasonably likely to predict clinical benefit to ensure that patients with serious and life-threatening diseases can access treatments while the expected clinical benefit is confirmed.

  For rare diseases that involve very small patient populations and heterogeneous presentation among other complicating factors, the approval of treatments based on surrogate endpoints is essential. These misguided coverage policies create heartbreaking access barriers for patients and families who have previously only known the pain that comes with having a rare disease for which there is no treatment, but now must cope with there being a breakthrough that they simply cannot benefit from. Payers, including self-insured plans, should not be allowed to base coverage policies on the pathway that was used to obtain FDA approval

- **Facilitate Access to Innovative Therapies by Removing Barriers to Value and Outcomes Based Payment Arrangements.** Value or outcomes-based purchasing agreements base payment for a therapy on the drug's performance and the patient's clinical outcome(s). They can change the way drugs are reimbursed in the United States, but there are old laws on the books that impede deep discounts from being offered by biopharmaceutical manufacturers to payers (both state Medicaid programs and private insurers). In an effort to update these old laws, CMS issued a rule that attempted to eliminate many of the barriers. While this rule was a start, federal barriers remain and are preventing these innovative payment arrangements from being successful at scale. The MVP Act would remove federal barriers that prevent state Medicaid programs, private payers, and manufacturers from entering value-based purchasing agreements by codifying and adding to provisions from CMS's Final Rule and adding value-based payment arrangements to the list of safe harbors to the federal anti-kickback statute. The bill would also require a GAO study on the effectiveness of VBPs on patient access, health outcomes, and health system costs.

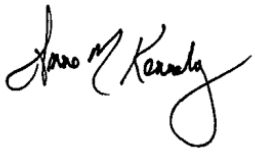
- **Enhance Access to Timely Diagnostics.** *The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study* released in 2023 by the EveryLife Foundation and Optum Health found that the mean diagnostic odyssey was more than 6 years, included up to 17 medical providers, and included avoidable costs ranging from $86,000 to $517,000. With the advent of diagnostic and newborn screening technology, timely diagnosis prevents catastrophic, irreversible disease progression, reduces costs, and opens the door to appropriate treatment and care when such options exist. In cases in which a disease can be reversed, stopped, or managed, overall costs to all parties – including government payers – can be lessened. With the advancement of disease modifying cell and gene therapies, the importance of facilitating near immediate treatment delivery will only continue to grow.

  We were pleased to see a provision enhancing access to genetic testing provision in the 2021 Cures 2.0 proposal and encourage its retention. Additionally, we encourage the adoption of a provision to enhance the data and technology infrastructure of the nation's newborn screening system to facilitate improved testing processes, quality, and results tracking, reduce disparity between states and within each state, assist programs in adopting new technologies, and help newborn screening programs across the country evaluate disease risk and improve their screening standards.

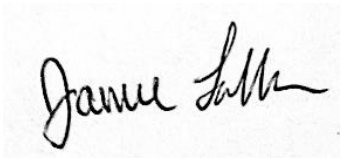
Thank you for your attention to our rare disease community's priorities. The EveryLife Foundation was founded to spur innovation for rare disease treatment through science driven public policy. The passage of the 21st Century Cures Act demonstrated that science-based policy fixes to the development and regulatory process could significantly impact efforts to unlock treatments for patients. We look forward to working with you to build upon the successes of this landmark legislation and to harness the potential of opportunities like Cures 3.0.

For additional information, please contact Jamie Sullivan, Vice President of Policy at the EveryLife Foundation for Rare Diseases at jsullivan@everylifefoundation.org or by phone at 202-445-4009.

Sincerely,



Annie Kennedy
Chief of Policy, Advocacy & Patient Engagement
EveryLife Foundation for Rare Diseases



Jamie Sullivan
Vice President of Policy
EveryLife Foundation for Rare Diseases

CC:
Michael Perlmutter, CEO
Vicki Seyfort-Margolis, Chair, Board of Directors
Frank Sasinowski, Vice-Chair, Board of Directors