November 17, 2025

The Honorable Senator Rick Scott and The Honorable Senator Kirsten Gillibrand
Senate Special Committee on Aging
United States Senate
Washington, DC 20510

Re: PDCD – A Life-Threatening Rare Disease in Need of FDA Regulatory Flexibility

Dear Senator Scott and Senator Gillibrand:

We write today in support of the U.S. Senate Special Committee on Aging's leadership and bipartisan commitment to advancing the development and approval of treatments for rare diseases. We commend the Committee for its continued oversight of the U.S. Food and Drug Administration's (FDA) efforts to enable innovation on behalf of the approximately one in 10 Americans living with a rare disease. Of the more than 10,000 identified rare diseases, fewer than 10 percent currently have an FDA-approved treatment -- underscoring the urgent need for flexible, patient-centered approaches to regulatory decision-making that expand access to lifesaving medical innovation for patients and families navigating life-threatening conditions.

Our five organizations represent patient advocacy groups dedicated to advancing research and supporting patients living with rare mitochondrial diseases. In our role as advocacy leaders, we have witnessed firsthand the urgent need for rare and ultra-rare disease therapies. In cases where no approved treatment exists, regulatory flexibility from the FDA can mean the difference between life and death for Americans facing these conditions.

A prominent example is the Pyruvate Dehydrogenase Complex Deficiency (PDCD) community, which was recently devastated when the FDA issued a Complete Response Letter (CRL) denying approval of a treatment called dichloroacetate (DCA).

PDCD is severe and life-limiting, causing seizures and neuromuscular decline, which robs children of basic developmental milestones and too often shortens life expectancy. It affects fewer than 1,000 children in the U.S., and there is currently no FDA-approved treatment. PDCD has only one management option – a ketogenic diet – which is extremely difficult to sustain long-term, can be harmful for some children, and is ultimately not enough to keep the disease's

severe consequences at bay. Families have long waited for a therapy that could change the course of this disease.

DCA has shown encouraging signs in clinical research studies. In a national Phase 3 clinical study, PDCD patients demonstrated a reduction in lactate, the primary biomarker of the disease. In longer trials, including open-label studies, DCA treatment has resulted in sustained developmental improvement and survival in children with PDCD. Critically, when compared to historic cohorts, treatment with DCA has substantially reduced mortality in patients with PDCD. DCA is also an incredibly safe, well-understood intervention. It has been studied as a treatment for mitochondrial diseases for nearly 50 years with very limited adverse events.

For the PDCD community, this issue is far more than data in a regulatory filing. It's about every child with PDCD – those we have tragically lost and those who are still fighting. It's about the parents who have seen their children "come back to life" and "move their body out of pure joy" in DCA clinical trials and who are terrified they will lose access to this therapy. It's about every PDCD family that is still waiting for hope.

When the FDA declined to approve DCA in September 2025, more than 80 leading researchers and clinicians in the mitochondrial disease space signed a joint letter of support urging the FDA to pursue an expedited, flexible regulatory path forward for DCA as the first and currently only potential treatment for PDCD. In addition, our five patient advocacy groups issued a statement expressing deep disappointment in the FDA's decision. Last week, a PDCD mom launched a petition that already has thousands of signatures.

Our advocacy efforts have focused on ensuring that the FDA considers the unique challenges of rare disease drug development – including extremely small pools of patients for clinical trials, variable and poorly understood natural history information, and the life-threatening and progressive nature of many of these diseases.

And while we share your enthusiasm for recent developments at the agency like the Rare Disease Evidence Principles (which DCA would have almost certainly fallen under if submitting today), we believe this DCA denial is the exact situation Congress envisioned avoiding when they granted the FDA additional tools and flexibility in the *21st Century Cures Act* (P.L. 114-255) and the *Accelerating Access to Critical Therapies Act* (P.L. 117-79). These authorities provide the agency with clear statutory flexibility to use surrogate endpoints, rely on real-world evidence, and consider the totality of evidence for small patient populations – all principles that align squarely with the scientific record supporting DCA.

To improve FDA decision-making processes for rare diseases in general, and specifically in the case of DCA for PDCD, we have encouraged the agency to engage directly with families, researchers, and clinicians to gain their insights on the effects of the investigational treatment and to better understand the impact of regulatory decisions on patient communities. We have also urged the agency to explore all available regulatory pathways, including expanded access, conditional approvals, or accelerated review.

We believe that addressing the needs of ultra-rare disease communities requires a balance of scientific rigor and compassion. A reconsideration of DCA for PDCD would reflect both. Accordingly, we respectfully urge the Committee to consider encouraging the FDA to convene a focused workshop or listening session with PDCD clinicians, researchers, and affected families to explore appropriate evidentiary standards and potential regulatory pathways for DCA and similar ultra-rare therapies.

Should Commissioner Makary grant the Committee's request, we respectfully urge you to use that opportunity to elevate the voices of the PDCD community. Please emphasize to the agency that the loss of access to DCA would have devastating consequences for the affected children and their families. There are real lives – and real hope – at stake. Thank you for your continued leadership and attention to this critical matter.

Sincerely,

United Mitochondrial Disease Foundation
MitoAction
Cure Mito Foundation
Hope for PDCD
Elizabeth Watt PDCD Research Fund