Dear Commissioner Makary,

We are physicians and researchers caring for patients with Pyruvate Dehydrogenase Complex Deficiency (PDC deficiency), and we are writing to seek your immediate intervention in the review process for sodium dichloroacetate (DCA), manufactured by Saol Therapeutics, for the treatment of PDC deficiency. PDC deficiency is a life-threatening inborn error of metabolism; the need for treatment for individuals with PDC is critically urgent and timely approval of disease-modifying treatment is of the essence.

Although PDC deficiency falls into the category of rare and orphan diseases, it is the single most common genetic mitochondrial disease in children, impacting an estimated 1,000 children in the United States. Children with PDC deficiency live with chronic, progressive disease. The PDC enzyme is integral to normal energy metabolism, providing sufficient adenosine triphosphate (ATP); PDC deficiency causes affected children to suffer energy failure that manifests principally in diminished intellectual and muscle function, as the nervous system and skeletal muscle are particularly dependent on an adequate supply of ATP. Additional manifestations of PDC deficiency include life-limiting metabolic acidosis, epilepsy (which may be intractable to other medications), and progressive neurologic disease including movement disorders, developmental delay and intellectual disability. As a result of these features, patients with PDC deficiency have a childhood mortality rate as high as 39%, with a mean age of death of 2.7 years.

The existing treatment practice for PDC deficiency is the ketogenic diet, a highly medicalized diet that comes with iatrogenic complications. Children with PDC deficiency on a keto diet continue to have very high medical needs, including recurrent hospital admissions, need for mobility devices to assist with ambulation and medical support for most activities of daily living. Therefore, there is major need for additional targeted therapies for PDC deficiency.

DCA is a targeted treatment for PDC deficiency. It demonstrably improves residual enzyme activity in PDC deficiency. In the recently completed national Phase 3 clinical trial - funded in part by the Orphan Products Division of the FDA and by the National Institute for Child Health and Development (NICHD) - the patients demonstrated a reduction of lactate, the primary biomarker of PDC deficiency. In longer trials, including open-label studies, DCA treatment has resulted in sustained developmental improvement in children with PDC deficiency. Critically, when compared to historic cohorts, **treatment with DCA has substantially reduced mortality in patients with PDC deficiency**.

We know that DCA is an incredibly safe intervention. Since it was first identified as a potential treatment for PDC deficiency in 1974, DCA has been experimentally used to treat mitochondrial diseases for nearly 50 years with numerous clinical trials on DCA in mitochondrial diseases as well as malignancy, with no adverse events, aside from reversible peripheral neuropathy that modern pharmacogenetics-based dosing has essentially eliminated.

We recognize the challenges of drug development in rare diseases and appreciate the FDA's stated commitment to regulatory flexibility in this space. We respectfully ask that the agency

work with Saol Therapeutics to find alternate routes to seek confirmatory evidence. PDC deficiency is a heterogeneous disease and no previously validated endpoints exist. The DCA Phase 3 clinical trial took an innovative risk, working with families to design a patient-reported outcome measure as its primary outcome. While an exciting step forward in measuring clinically meaningful endpoints, this endpoint only measured improvement in a subset of patients because of the intrinsic heterogeneity of the disease.

Given this, we seek full or accelerated approval for DCA without another trial. **An additional randomized controlled clinical trial is financially impossible for the drug sponsor and would result in DCA being no longer available to patients.** This will result in **unnecessary deaths, irreversible developmental decline, and health complications** for these vulnerable children. More broadly, as a rare disease community, we need faster and more flexible regulatory pathways to approve safe, promising treatments and advance more patient-centered outcome measures. Without this, many rare diseases will remain incurable.

We are asking the FDA leadership to revisit this decision and grant full or accelerated approval without the need to conduct another trial. Every day of delay has real, measurable consequences for Americans with PDC deficiency in unnecessary mortality, irreversible decline, and lost hope for families.

Sincerely,

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