Congress of the United States

Washington, DC 20510

October 24, 2024

The Honorable Robert Califf, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Califf:

We write regarding the administration of the Food and Drug Administration's (FDA's) Rare Pediatric Priority Review Voucher (PRV) program, particularly as it applies to innovative treatments like gene therapies.

For the Sickle Cell Disease (SCD) community, the December 2023 approvals of the first gene therapies to treat SCD was the culmination of decades of hard work – a collaboration including patients, providers, researchers, manufacturers, and FDA. In its announcement, FDA officials rightly noted the potential to do more for other rare disease patients: "[g]ene therapy holds the promise of delivering more targeted and effective treatments, especially for individuals with rare diseases where the current treatment options are limited."

SCD is an inherited blood disorder that affects an estimated 100,000 individuals in the United States. The disease can result in multiple medical complications and cause acute and chronic episodes of severe pain. For the approximately 20,000 patients with the most severe form of the disease, these approvals offer a transformative new tool in the treatment options for patients. However, getting these treatments to patients comes with a separate set of challenges. We have been grateful to see FDA officials recognize these challenges for some time, and we need to ensure that we are pulling all the levers available to us to support this fragile rare disease innovation ecosystem.

Congress established the Rare Pediatric Disease Priority Review Voucher (PRV) Program in 2012 to provide one of those very levers. The PRV Program was intended to incentivize the development of novel therapies for rare pediatric diseases by providing a "priority" 6-month review of another new drug application. At the time, one of the bill sponsors noted that, the program will, "incentivize pharmaceutical companies to develop new drugs for children with rare pediatric diseases, such as childhood cancers and *sickle cell disease*, by expanding the cost-neutral priority review voucher program."

However, we are concerned that FDA's recent administration of the program may not be fulfilling the program's promise, original vision, and intent. Specifically, we understand that FDA has made an initial decision to narrowly interpret the definition of "active ingredient" in the PRV statute, resulting in the unexpected denial of at least one pediatric PRV. To receive a PRV, the product must contain "no active ingredient that has been previously approved in any other

application." Congress did not define the term, "active ingredient" in the statute, but in regulations, FDA defines it as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that *may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form* intended to furnish the specified activity or effect."

Congress included this requirement to prevent potential manufacturers from receiving PRVs for "simply making small tweaks to old drugs." Small, non-innovative tweaks that do not require substantial investment and testing are therefore rightfully excluded from consideration for PRVs; however, the development of these complex gene therapies to treat an entirely new disease affecting thousands of patients can hardly be considered a "small tweak" to an "old drug." FDA is responsible for determining whether medicines are safe and effective, and approval decisions should be appropriately insulated from the political process.

However, the decision whether to narrowly or broadly interpret the definition of "active ingredient" for purposes of awarding a PRV is not so much a question of science as it is one of policy. Congress has not provided guidance as to how FDA should determine if two active ingredients in an ex-vivo gene therapy are the same or different, but the text of the statute and the legislative history make clear that Congress wanted to create an incentive to treat patient populations that might not warrant investment if left simply to ordinary market forces. By interpreting this statutory requirement in a narrower way than the statute requires – and one that flies directly against Congressional intent – we risk disrupting this delicate ecosystem, jeopardizing not only the availability of SCD treatments today, but also investments in complex and life-saving innovation for the future.

We understand that FDA may be in the process of reconsidering its interpretation. This decision is critical for the future of rare disease drug development and rare disease patients, and we are grateful for the FDA's close attention to this matter. We hope that you will keep these additional considerations in mind as you conduct your review.

Sincerely,

Tim Scott
U.S. Senator

Danny K. Davis
U.S. Representative

Copy:
Dr. Peter Marks, Director, Center for Biologics Evaluation and Research