ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

May 23, 2022

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry (Docket No. FDA–2021–D–0398)

To whom it may concern:

The American College of Medical Genetics and Genomics (ACMG)[1] appreciates the opportunity to provide feedback on the Human Gene Therapy Products Incorporating Human Genome Editing Draft Guidance for Industry. We support the overarching goal of providing guidance on this topic and appreciate the attention to the importance of studying on-target and off-target genome editing (GE) in preclinical studies; in vitro human cell models appropriate for GE preclinical studies; the value of patient cell models for in vitro studies; and components of GE agents, including methods of GE and of delivery.

## IV. CONSIDERATIONS FOR PRECLINICAL STUDIES

We remain concerned about potential delays in GE development that could result from possibly uninformative or duplicative preclinical studies and recommend that the guidance elaborate on the use of human-derived cell or organoid models in place of less relevant animal genomes. For example, the studies of off-target effects done *in vivo* in animal models do not predict off-target effects in the

[1] The ACMG is the only nationally recognized medical professional organization solely dedicated to improving health through the practice of medical genetics and genomics, and the only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization. The ACMG is the largest membership organization specifically for medical geneticists, providing education, resources and a voice for more than 2,500 clinical and laboratory geneticists, genetic counselors and other healthcare professionals, nearly 80% of whom are board certified in the medical genetics specialties. ACMG's mission is to improve health through the clinical and laboratory practice of medical genetics as well as through advocacy, education and clinical research, and to guide the safe and effective integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health.



7101 Wisconsin Avenue
Suite 1101, Bethesda, MD 20814
Telephone: 301-718-9603
Fax: 301-718-9604

**www.acmg.net**

human genome. This is because the nucleotide sequences that target specific human genes during genome editing would have entirely different interactions with the genome of an animal model. Therefore, off-target effects can be assessed in a human cell model, often *in vitro*. Requiring *in vivo* modeling to assess off-target effects from genome editing would delay implementation of genome editing. Furthermore, we are concerned that routine use of a surrogate species-specific agent would use different nucleotide sequences with different effects in an animal model than the GE agent would have in the human genome, rendering the study irrelevant in many cases to the effects in the human genome with regard to on-target effects and truly irrelevant with regard to off-target effects. Therefore *in vivo* toxicity studies should not be required each time nucleotide sequences are changed, since these effects are better studied *in vitro* in human cells.

## V. CONSIDERATIONS FOR CLINICAL STUDIES

Many diseases that may be well-suited for a GE product are lethal in children or are progressive such that treatment later in life would have limited benefits. Therefore, we are also concerned that recommending for adult and then adolescent cohorts in clinical trials prior to enrollment of children might delay GE development, especially for lethal disorders where no adult and few adolescent patients are available to be enrolled. The guidance should be expanded to recognize this reality and the need to start such trials in younger children.

### Future opportunities for efficient preclinical studies

Some elements of GE will be shared between agents, such as a delivery method including an AAV vector. There might be efficiencies to be gained where a GE agent could be studied *in vivo* initially, and later applications of a similar GE agent might only require preclinical toxicity studies focused on *in vitro* human cell models. This type of approach could allow the more efficient and timely development of new GE treatments. The goal of such efficiencies would be making life-saving treatments available to rare disease populations in a more timely and cost-effective manner.

As our experience with gene edited therapeutics improves, and additional data is gathered, there exists an opportunity to improve the efficiency of moving such therapeutics into clinical trials. This guidance should be updated on a regular basis to reflect evolving clinical trial models to get innovative therapies to patients faster. This includes those for ultra-rare genetic conditions that currently have no treatment, including those in which patient populations may be in the single digits. For example, use of human organoid or other non-animal models for



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toxicology studies could be considered. In situations where a therapy only varies in genetic sequence when compared to another therapy already in trial, models should be considered that leverage existing data so that toxicology studies may be streamlined for subsequent variations.

Sincerely,

Marc Williams, MD, FACMG
President
American College of Medical Genetics and Genomics




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**www.acmg.net**