Innovative Genomics Institute

June 9th, 2022

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

Re: Docket Number FDA-2021-D-0398: **Human Gene Therapy Products Incorporating Human Genome Editing: Draft Guidance for Industry**

The Innovative Genomics Institute (IGI) is pleased to submit the attached comments in response to the issuance by the Food and Drug Administration ("FDA") of a request for comments in its Federal Register Notice entitled "Human Gene Therapy Products Incorporating Human Genome Editing: Draft Guidance for Industry" (hereinafter, the "Draft Guidance" or "guidance"). We are grateful to the FDA for preparing a Draft Guidance that addresses products created by Gene Editing (GE) technologies and appreciate the opportunity to contribute our expertise to the regulation of these therapies.

The Innovative Genomics Institute (IGI) is a non-profit, academic research organization formed through a partnership between the University of California, Berkeley and the University of California, San Francisco, two of the world's leading scientific research institutions. After co-inventing CRISPR-based systems for rewriting DNA, Jennifer Doudna founded the IGI to bring together researchers in diverse disciplines with a powerful combined expertise in order to apply this technology to address some of humanity's greatest problems. In addition to our efforts in the life sciences, the IGI is committed to advancing scholarship on the ethical, legal, and social impacts of this transformational technology. We have approached these comments on the FDA's Draft Guidance in a similar interdisciplinary vein.

We appreciate your consideration and are happy to discuss further if desired.

On behalf of the Innovative Genomics Institute,

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Genome editing (GE) therapies hold the promise to drastically improve our approach to treating human disease with the potential to provide radically new therapies and cures for previously untreatable conditions. Importantly, GE therapies offer an opportunity to create therapies that are bespoke, affordable, and accessible at scale. Given the large potential benefits of GE therapies, we are heartened by the care and attention the FDA has shown in recent guidance documents and other communications. However, we seek clarification regarding the FDA's thinking about the potential for CRISPR GE therapies as a platform technology and the manufacturing requirements set out by this guidance, particularly for ex vivo GE therapy. We also seek additional guidance regarding study populations for conditions for which therapies exist but are suboptimal, and we request greater specificity on conventional cell and gene therapy versus GE therapy guidelines.

We ask the FDA to provide more specific and tailored guidance and recommendations for drug substances and products created by GE technologies, particularly those therapeutics that are created ex vivo using editing reagents that are not intended to persist (for example, purified Cas9 protein in complex with its guide RNA). By identifying CMC requirements tuned to the particular risks presented by the drug substances and products created by this GE approach, the FDA can better assure a demonstration of product safety, identity, quality, purity, and strength (including potency) without imposing undue or unnecessary burdens on sponsors of therapeutics that provide important patient and public health benefits.

GE as a Platform Technology

A key benefit of CRISPR-based GE therapies is the modularity of the technology. Targeting a new gene or gene locus could require only a change in the sequence of the guide RNA; the Cas protein structure is constant and guide function remains unchanged. Conceivably, a single platform could be developed to treat different indications in a category of disorders (e.g. hematological conditions) and the entire pipeline could remain the same with only a change in guide RNA sequence. This represents a fundamental change in drug development and one with implications beyond CRISPR GE therapies to other nucleic acids-based drugs such as RNA vaccines.

This modularity, and the potential for GE therapies to treat a wide range of human diseases, provides a real opportunity to create accessible therapies by streamlining the process and requirements for an IND. Ideally, a sponsor could cross-reference previous INDs and leverage the modularity of this approach to rapidly create a wide range of effective therapies following validation and approval of a GE platform. The current guidance does not reference this aspect of GE therapies and we suggest that the FDA consider including language that aids sponsors in taking advantage of this unique feature of GE therapies.

Indeed, the NIH has begun funding work in this area through the Platform Vector Gene Therapy Pilot Program, led by NCATS. The modularity of GE therapies is particularly exciting for the prospect of developing therapies, at a reasonable cost, for rare conditions, which occur at a high frequency (1 of every 100-200 live births). Given the novel nature of platform-based drug development, we also recommend the FDA consider investing in studies that will improve our understanding and the needs for regulation of platform technologies.

CMC Considerations

On lines 192-193, the FDA makes it clear that for in vivo GE therapies, the final drug product (DP) is the plasmid or vector encoding the GE component; however, similar clarity for ex vivo GE therapies is lacking. We recommend the FDA state that the final DP is represented by the modified cells re-formulated for injection into the patient; the modified cells represent the drug substance and that the GE components used to modify the cells (Cas protein, guide RNA etc) are ancillary materials that could be accepted under a rigorous Certificate of Analysis for high quality research grade rather than manufactured under cGMP.

The rationale for explicitly removing the GE components from the designation of a DP in ex vivo GE therapies is that these components are not a part of the final product infused into patients. Without the presence of transgenes encoding the GE components, natural cellular processes degrade the GE components (1, 2). Furthermore, reagents such as Cas9 and guide RNA are non-viral, pure agents. As compared to other reagents such as sera, Cas9 and guide RNA are not complex mixtures, do not exhibit high batch-to-batch variability, and are not animal-derived. The guide RNA is often synthesized chemically with no exposure to animal tissues or microbial agents, thus limiting the possibility of adventitious biological agents or contaminants.

As purified agents, the guide RNA and Cas9 protein are readily amenable to testing for the four required characteristics of the critical reagents as identified by the FDA: identity, purity, potency, and safety. Where manufacturers or sponsors can use a technique such as mass spectrometry to test the identity and purity of the critical reagents, additional compliance requirements for manufacturing (e.g. cGMP) during early stages of clinical trials are unlikely to lead to a material increase in safety to the research subject.

Preclinical Studies & Off-Target Edits

On lines 423-425, the FDA specifies that the clinical cell source should be used for preclinical data. We would ask the FDA to expand on their thinking for indications that involve whole organism systems, such as hematological conditions, and the use of human cells in animal models.

Similarly, in off-target editing assessments in preclinical studies, we would ask that the FDA consider titrating the acceptability of levels of off-target edits by cell type, taking into consideration the relative background genomic modifications undertaken by the cell type and the potential for tumorigenicity.

Study Populations

On lines 512-515, the FDA states “Human GE products may have significant risks and an uncertain potential for benefits. Therefore, first-in-human trials involving such products generally should be designed to enroll only subjects for whom no other treatment options are available or acceptable.” However, many GE therapies are, and will be, developed for conditions in which there are clinically acceptable therapies, such as hydroxyurea for sickle cell disease, but for which a GE approach may yield a more durable or safer therapeutic option. We recommend the FDA clarify what constitutes an appropriate study population for conditions in which non-GE treatment options are available but may be suboptimal and develop guidelines for such situations.

Considering Cell and Gene Therapy as GE Comparator

In several sections of the draft guidance (e.g. lines 356-359, 503-504, and 536-540) the FDA suggests following previous guidelines developed for conventional cell and gene therapies. We are concerned by a general recommendation to follow conventional cell and gene therapy guidelines for GE therapies as these two modalities exhibit different risk profiles, particularly for ex vivo GE therapies. Cell and gene therapies are the closest comparators for GE therapies, but key differences relevant to safety are elided in this draft guidance document.

The safety concerns regarding conventional cell and gene therapies are often centered around concerns of insertional mutagenesis and the use of viral vectors to deliver the product. In contrast, modifications from ex vivo GE therapies are predictable with the potential for off-target effects to be robustly de-risked. Rather than randomly augmenting cells with a transgene, one of the virtues of gene editing is its ability to directly target an endogenous gene, providing consistent and predictable expression levels, and thereby reducing the risk of genotoxicity.

Given this, we are concerned that reliance on past guidances for non-GE cell and gene therapies may overestimate the risks involved in ex vivo GE therapies and will not take advantage of the programmable nature of CRISPR based genome modifications. We would encourage the FDA to explicitly differentiate the risks, and the necessary supporting safety data, for ex vivo GE, in vivo GE, and conventional cell and gene therapy accounting for differences due to the use or non-use of viral vectors.

References

1. Kimberland ML, Hou W, Alfonso-Pecchio A, et al. Strategies for controlling CRISPR/Cas9 off-target effects and biological variations in mammalian genome editing experiments. *Journal of Biotechnology*. 2018;284:91-101. doi:10.1016/j.jbiotec.2018.08.007.
2. Tycko J, Myer VE, Hsu PD. Methods for Optimizing CRISPR-Cas9 Genome Editing Specificity. *Molecular Cell*. 2016;63(3):355-370. doi:10.1016/j.molcel.2016.07.004.