



1 September 2026

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2026-D-1257, Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing; Draft Guidance for Industry

To whom it may concern:

The International Society for Stem Cell Research (ISSCR) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance for Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing.

The ISSCR is an independent, global, nonprofit organization that promotes excellence in stem cell science and applications to human health. ISSCR represents 4,700 scientists, educators, ethicists, and business leaders across 80 countries. Our vision is a world where stem cell science is encouraged, ethics are prioritized, and discovery improves understanding and advances human health. Additional guidance from the FDA will help our members, who are at the forefront of research and innovation, in their work. To complement FDA's initiatives and foster progress in this field, we offer the following comments and recommendations:

I. General Comments

- 1. Safety and Quality Considerations.** ISSCR suggests that FDA consider incorporating several additional safety and quality considerations into the guidance. These considerations are particularly relevant to ex vivo genome-edited cell-based gene therapy products, genome-editing platforms involving delivery of DNA or other persistent nucleic acid components, and editing strategies involving multiple genomic loci. See line comments below.
- 2. Similarity-Based Provisions.** Several provisions permit leveraging where products are similar or comparable, without identifying the attributes that establish similarity, the magnitude of difference that defeats it, or the data that would support a similarity determination. This may result in routine questions being resolved through individual sponsor-agency interactions rather than through the guidance itself. ISSCR suggests that FDA include product attributes relevant to each leveraging pathway and provide examples that would support leveraging.



- 3. Identity-based provisions.** Leveraging genotoxicity data requires a stricter identity-based standard. However, in some cases — particularly for off-target safety data — underlying scientific rationale for leveraging using a similarity standard may still be appropriate with justified differences (such as minor changes in formulation, such as PEG-lipid molar ratio adjustments made for pharmacokinetic tuning, which would not meaningfully affect the genotoxic risk profile). ISSCR suggests including clarification regarding cases in which a similarity-based standard with appropriate based justification could replace an identity-based standard.

Thank you for considering our views on the draft guidance for Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing. If the ISSCR can clarify any of these views or be of assistance, please contact Tyler Lamb, ISSCR's Director of Policy at tlamb@isscr.org or Denise de Villa, ISSCR's Manager of Policy at ddevilla@isscr.org.

Respectfully submitted,

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II. Specific Comments

Section (Line)	Issue	Proposed Change
I. Introduction		
22 - 25	The draft guidance states: "This guidance also provides recommendations on how sponsors may consider leveraging prior knowledge to increase review efficiency and accelerate product development across multiple programs. These recommendations include how to leverage chemistry, manufacturing, and controls (CMC); nonclinical; and clinical prior knowledge." It would be helpful to clarify that leveraging prior knowledge may improve efficiency, but does not lessen the sponsor's responsibility to demonstrate product-specific safety, quality and clinical relevance.	ISSCR recommends adding the following language: "Leveraging prior knowledge may reduce the need for certain de novo studies where scientifically justified, but sponsors remain responsible for establishing the safety, quality, and clinical suitability of each individual product."
III. Knowledge for Potential Leveraging		
	The draft guidance repeatedly permits leveraging of prior knowledge when products or components are "sufficiently similar" or "highly similar," but does not define similarity thresholds or provide a framework for making this assessment. This ambiguity can create significant uncertainty for sponsors, who may be unable to predict whether FDA will accept a leveraging rationale until late in the review process — potentially discouraging leveraging altogether and undermining the guidance's goal of reducing unnecessary duplicative testing.	ISSCR suggests that FDA provide a decision-tree, comparability matrix, or illustrative example for the CMC and nonclinical sections, showing what would and would not be accepted as "sufficiently similar," even if presented as non-binding illustrative examples rather than fixed criteria.

A. Chemistry, Manufacturing, and Controls		
Section III.A.1.c, Section III.A.2, and Section III.B.2	The draft guidance emphasizes off-target editing and genomic-integrity assessment for GE products. However, the risk profile of the genome-editing system may differ substantially depending on how the editing components are delivered. Specifically, delivery platforms involving DNA or other nucleic-acid modalities capable of prolonged intracellular persistence may introduce an additional safety consideration: unintended integration or persistence of exogenously delivered sequences, including donor DNA, vector sequences, expression cassettes, transgenes, or other components of the editing system. These risks are mechanistically distinct from conventional nuclease off-target activity and may not be adequately assessed by assays designed solely to identify unintended cleavage or sequence alterations at nominated off-target sites.	ISSCR suggests that FDA consider explicitly recognizing delivery modality as a factor when determining the appropriate scope of genomic-integrity assessment.
III.A	It would be helpful to understand the minimum elements of a leveraging justification and clarify that leveraged CMC information should be supported by a similarity in impact and assessment.	ISSCR requests that FDA provide clarity regarding the minimum elements required to leverage CMC information.
III.A.1	It would be helpful to understand when product-specific verification is expected, and which method characteristics may need to be re-assessed when test articles differ.	ISSCR requests that FDA provide more information regarding expectations for product-specific verification (e.g. assessment of differences in sequence, matrix, formulation, concentration range, or intended use - all of which may affect method performance.)
III.1.A.c III.B.2	When multiple loci are simultaneously targeted, concurrent DSBs may create opportunities for inter-	ISSCR recommends adding the following language to Section III.A.1.c and/or Section III.B.2:

(191 – 202 and 588 – 718)	locus chromosomal rearrangements, including reciprocal or non-reciprocal chromosomal translocations, large deletions, inversions, or other structural variants. This consideration may be particularly important when the targeted loci are duplicated or highly homologous genomic regions, or when multiple copies of related genes are intentionally targeted. An example of this can be the human TRBC1/2 loci for CAR-T engineering.	“For GE strategies involving simultaneous targeting of more than one genomic locus, sponsors should consider the potential for inter-locus chromosomal rearrangements, including translocations, inversions, large deletions, or other structural variants resulting from concurrent DNA double-strand breaks. This consideration may be particularly relevant when targeting duplicated or highly homologous genomic loci or when multiple genomic sites are intentionally edited. Where scientifically appropriate, additional genomic-integrity assessments capable of detecting such structural alterations should be considered. Depending on the product and editing strategy, such assessments may include targeted genomic assays, digital PCR-based approaches, whole-genome sequencing, long-read sequencing, or other appropriately validated methods.”
III.A.3.a.i (253 – 259) Table 1	The recommendation is to allow data leverage from “other mRNA components or products that code for a different nuclease”. However, RNA length, secondary structure, GC content, and terminal elements (5’ or 3’) can affect RNA stability. mRNAs that encode different nucleases can have similar stability in vitro given similar length, structural features. However, their stabilities could be very different in vivo. Therefore, it may not be appropriate to leverage mRNA stability data from one nuclease to a different nuclease.	ISSCR recommends adding the following language (in bold) to the current paragraph: “For example, for the stability of an mRNA that encodes a nuclease it may be appropriate to leverage other mRNA components or products that code for a different nuclease, providing that RNA length, terminal elements, and RNA modifications are comparable.”

B. Nonclinical		
III.B (392 – 398)	While several examples of areas for leveraging data are included, there is no information regarding when or if leveraging would be sufficient for clinical entry or when product specific nonclinical work may still be expected.	ISSCR suggests including information and examples illustrating when leveraging may be sufficient for early clinical entry and when product-specific nonclinical work may still be expected.
III.B.1.b.2 (464 – 490)	The draft guidance appropriately discusses leveraging biodistribution data to identify representative human tissues and cell types that may warrant further assessment for on-target and off-target editing. The guidance also specifically discusses the use of biodistribution data concerning the gonads to inform DART and germline-transmission assessments. A similar principle could be applied to the central nervous system (CNS). For cell-based GE products that are not intended to target the CNS, unintended migration or distribution of administered cells into the brain or spinal cord could represent an important safety consideration. Conversely, for products specifically intended to target the CNS, CNS distribution would be an intended product attribute and should be evaluated accordingly.	ISSCR suggests that FDA consider adding CNS in addition to gonads as an area of concern for unintended editing and/or migration of GE cells, with appropriate restrictions.
	The recommendation is to allow biodistribution data leverage from prior studies provided that LNP composition and characteristics are similar. It has become more apparent that inflammatory state and other plasma proteins related to specific diseases can affect biodistribution and targeting of LNP in vivo.	ISSCR requests FDA to clarify if additional assessment may be needed for applications in which lipid uptake or inflammation might be altered due to underlying disease

III.B.1.c.ii.1 (528 – 542)	This section requires that all LNP lipid components (ionizable lipid, cholesterol, PEG-lipid) be identical in both type and ratio to leverage genotoxicity data — a materially stricter, identity-based standard than the similarity-based standard applied elsewhere in the guidance (e.g., CMC, general nonclinical). This inconsistency may not be scientifically justified in all cases, particularly where minor formulation differences (e.g., PEG-lipid molar ratio adjustments made for pharmacokinetic tuning) would not meaningfully affect the genotoxic risk profile.	ISSCR requests FDA to clarify whether a similarity-based standard could apply to genotoxicity leveraging when sponsors can demonstrate that formulation differences do not affect particle physicochemical characteristics or impurity profiles relevant to genotoxic risk, consistent with the standard used for other CMC and nonclinical leveraging determinations.
III.B.2.e.iii (715 – 718)	The guidance permits leveraging of off-target assessment methods, assay parameters, and NGS/bioinformatics pipelines across products, but explicitly states that off-target data itself is generally not appropriate to leverage across products using different gRNAs. Because gRNA/target selection is typically the primary variable that changes between new development programs, this limits the practical burden reduction: the most resource-intensive component of off-target safety assessment — functional confirmatory testing — must still be repeated for nearly every new product.	ISSCR requests FDA to clarify whether any partial leveraging is feasible for gRNAs with high sequence homology, shared seed sequences, or the same PAM requirements, short of full sequence identity.