# Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing; Draft Guidance for Industry

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# Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing

# Draft Guidance for Industry

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Biologics Evaluation and Research**
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## Draft Guidance for Industry

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## I. INTRODUCTION

We, the FDA, are issuing this draft guidance to assist you (manufacturers, applicants, and other stakeholders) in developing human gene therapy (GT) products incorporating ex-vivo and in vivo genome editing (GE)[1] of human somatic cells (GE products). Specifically, this guidance reflects FDA's current thinking on the type of prior knowledge (i.e., public and platform knowledge)[2] that may be scientifically appropriate to leverage[3] to advance product development. 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. The ability to leverage prior knowledge to expedite product development may be particularly helpful in the context of GE products intended to treat rare diseases, many of which may be serious and life threatening.

This guidance is being released as part of a PDUFA VII commitment to publish guidance on leveraging prior knowledge for cell and GT (CGT) products. While this draft guidance specifically focuses on GE products, some of the recommendations, when finalized, are or may be applicable to other CGT products, such as adeno-associated viral (AAV) vectors, nanoparticle-based GT products, and ex vivo-modified cell-based GTs that do not incorporate GE. However, additional considerations may also apply to these related product types, based on the specific product and manufacturing process, that are beyond those recommended in this guidance.

[1] For the purposes of this guidance human GE is a process by which DNA sequences are added, deleted, altered or replaced at specified location(s) in the genome of human somatic cells, ex vivo or in vivo, using nuclease-dependent or nuclease-independent GE technologies.

[2] "Prior knowledge," "public knowledge," and "platform knowledge" are further defined in section II.

[3] For the purpose of this guidance, leveraged knowledge is used to fully or partially alleviate the need to generate new information/data.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should in* FDA's guidance means that something is suggested or recommended, but not required.

## II. BACKGROUND

As the development of GE products increases, so does the amount of knowledge available to support multiple aspects of product development. This prior knowledge may be scientifically appropriate to leverage in product development programs to streamline submissions and subsequent review of regulatory applications, and to expedite product development. For the purposes of this guidance, the following terms are defined as follows:

- "Public knowledge" or "generally accepted scientific knowledge" refers to medical or scientific information that is generally accepted by experts qualified by scientific training and experience in the relevant field including FDA experts[4] (e.g., certain data and information published in rigorous peer-reviewed publications). Generally, "prior knowledge" or "generally accepted scientific knowledge" is based on widely accepted scientific principles that are typically long-standing.

- "Platform knowledge" refers to knowledge gained from developing and manufacturing similar products and processes.[5] A platform is a well-understood and reproducible technology(s) applied to the development of a GE product that consists of the same or highly similar features across development programs. A platform may include, but is not limited to, manufacturing processes, mechanism of action (e.g., editing method), delivery method (e.g., lipid nanoparticle; LNP), or a combination of any such technologies. Platform knowledge may also be widely available; however, it may be proprietary and submitted to FDA by its owner and thus may require permission from the owner of the knowledge to leverage.

[4] For further information about generally accepted scientific knowledge, see "Generally Accepted Scientific Knowledge in Applications for Drug and Biological Products: Nonclinical Information- Draft Guidance for Industry (May 2023), available at https://www.fda.gov/media/168408/download. When finalized, it will represent FDA's current thinking on the topic. It may be possible for prior knowledge or generally accepted scientific knowledge "to be based on a sufficiently large volume of scientific studies/information that would be applicable beyond the specific instances in which that information was developed." *See Id.*

[5] FDA's use of the term "platform" in this guidance differs from the of the use of the terms "platform technology" and "designated platform technology" that are set forth in Section 506K of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356k) that was added by the PREVENT Pandemics Act, which was enacted as part of the Consolidated Appropriations Act, 2023 (Public Law 117-328). FDA recommendations about leveraging "platforms" in this guidance are not intended to apply to the platform designation process under Section 506K.

- "Prior knowledge" refers to public knowledge and/or platform knowledge. Additional guidance on how to leverage different kinds of prior knowledge is provided in section IV of this guidance.

Platform knowledge may include:

- Internal company platform knowledge (e.g., data generated by a sponsor from their own previous products using the same or similar manufacturing platforms). For example, a company that has developed multiple chimeric antigen receptor T cell (CAR T) products using the same cell expansion platform may consider leveraging process parameters, analytical methods, and manufacturing data across their product portfolio.

- Third-party platform knowledge submitted to FDA via master files (e.g., data generated by Contract Development and Manufacturing Organizations (CDMOs), raw material suppliers, or technology platform providers). For example, a CDMO operating standardized cell processing equipment can maintain a master file that multiple sponsors may seek to reference.[6]

- Publicly available platform knowledge (e.g., generally accepted scientific knowledge that could include published scientific literature, regulatory guidance documents, pharmacopeial monographs (USP, EP), and industry standards). For example, sponsors may leverage non-proprietary, publicly available CMC data to inform and justify their selection of critical reagents for drug product manufacturing or methods by referencing existing scientific literature, pharmacopeial monographs, and databases.

- Consortium and data-sharing initiative knowledge (e.g., collaborative efforts between academic institutions, industry, and stakeholders). For example, public-private initiatives may share knowledge that supports regulatory submissions by providing reference ranges for drug substance/drug product critical process parameters (CPPs).

The scientific soundness of leveraging prior knowledge depends on multiple factors. For example:

- The scientific soundness of leveraging CMC knowledge may depend on the similarities in the molecular structure of a component[7] or product and its manufacturing process (including the facility and equipment operating conditions).

[6] For biologics license applications (BLAs), sponsors must reference master files consistent with 21 CFR 601.2(g).
[7] FDA's guidance entitled, "Human Gene Therapy Products Incorporating Human Genome Editing" (January 2024) defines component as any material that is essential for the intended genomic modification, including those that may not appear in the final drug product. GE components may include, but are not limited to, the editor, DNA targeting elements (i.e., elements used to dictate the target DNA sequence, such as guide RNA) and a donor DNA template (i.e., DNA sequence provided to repair the target sequence), if applicable.

- The scientific soundness of leveraging nonclinical data for ex-vivo genome edited cell-based gene therapy products (ex-vivo GE products) may depend on the similarity in on-target genomic edits between products, cell source(s), manufacturing processes, formulation, and intended therapeutic mechanism. For in vivo GE products, the similarities and differences between the products, manufacturing process, final formulation, route of administration (ROA), proposed clinical dosing regimen, and dose levels will inform the ability to leverage data.

- The scientific soundness of leveraging clinical data may depend on various factors such as the similarities between the products, similarities between the diseases to be treated, the phase of clinical studies, the type of data being leveraged and the purpose of leveraging data (such as to support the initiation of a new clinical trial or to support a future licensing application).

- When determining whether knowledge can appropriately be leveraged, in many cases, developers could consider whether the knowledge applies to independent or dependent attributes of the component or product. Knowledge that pertains to attributes that may be independent of the component or product itself (e.g., an analytical method) may be easier to leverage than knowledge that pertains to dependent attributes (e.g., product activity/potency or identity).

Note, the recommendations provided in this document are not exhaustive. It may be possible to leverage additional types of prior knowledge. Sponsors should submit any leveraging proposals to FDA for consideration, and, if desired, discussion (see section IV). Furthermore, it may be possible to leverage additional knowledge throughout the product lifecycle as product specific experience and knowledge in the field is gained. However, in all cases, when leveraging any kind of prior knowledge, a sponsor should provide a justification for the applicability of the data being leveraged.

Additional recommendations, also applicable to GE products, can be found in other FDA guidance documents. For general recommendations on GE product design and manufacturing, nonclinical evaluations and the design of prospective early phase human clinical trials, we refer to FDA's guidance entitled, *"Human Gene Therapy Products Incorporating Human Genome Editing"* January 2024.[8] For further guidance on platform technology designation, we refer to FDA's draft guidance entitled, "*Platform Technology Designation Program for Drug Development*" May 2024.[9] However, please note that platform technology designation is not needed in order to leverage prior knowledge within or between product programs or between applications.

[8] FDA Guidance for Industry "Human Gene Therapy Products Incorporating Human Genome Editing" (January 2024), available at Human Gene Therapy Products Incorporating Human Genome Editing | FDA

[9] FDA Draft Guidance for Industry "Platform Technology Designation Program for Drug Development" (May 2024), available at Platform Technology Designation Program for Drug Development | FDA. When final, this guidance will represent the FDA's current thinking on this topic.

## III. KNOWLEDGE FOR POTENTIAL LEVERAGING

### A. Chemistry, Manufacturing, and Controls

Multiple types of CMC knowledge may be considered for potential leveraging throughout a product's lifecycle. This includes analytical methods, method validation, lot release specifications, stability data, comparability data, and process development and process validation data. The scientific soundness of leveraging prior knowledge will depend on multiple factors. For example, it may depend on the similarities in molecular structure of a product or genome editing component[10], similar cell source (for ex-vivo modified products), formulation, its manufacturing process (including the facility and equipment operating conditions) and intended therapeutic mechanism. If differences exist, an assessment should be performed to determine if these differences may preclude the use of all or part of the prior knowledge in a given instance, and consider the degree of differences and the level of potential impact on product safety and efficacy.

Examples of the types of CMC prior knowledge that may be considered for potential leveraging and how to assess the scientific appropriateness of leveraging are provided below (reference Table in Section IV).

1. Analytical methods and method qualification and validation data

   a. The use of platform analytical procedures, as defined in ICH Q2(R2),[11] may reduce the qualification and validation[12] burden.

   b. Platform analytical procedure qualifications and validations may be performed using a single component or product and applied to other similar components or products.

      i. The appropriateness of applying a platform qualification and validation may depend on the similarity between the test articles, particularly as it relates to qualities that may affect method performance. For example, different gRNA[13] sequences or sample matrices may impact performance of a purity assay.

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[10] See Footnote 7

[11] Per ICH Q2(R2), a platform analytical method is a multi-product method suitable to test quality attributes of different products without significant change to its operational conditions, system suitability and reporting structure. This type of method would apply to molecules that are sufficiently alike with respect to the attributes that the platform method is intended to measure.

[12] Assay qualification involves determining the assay's performance characteristics (e.g., accuracy, precision, specificity, and sensitivity). Assay validation should confirm the performance characteristics of the fully-optimized assay by comparing assay performance during the validation study to appropriate pre-specified acceptance criteria for accuracy, precision, specificity, and other relevant performance characteristics. See also 21 CFR 211.165(e) and 211.194(a)(2).

[13] "gRNA" refers to guide RNA, an RNA molecule that directs Cas nucleases to precise genomic targets by hybridizing to complementary DNA sequences through Watson-Crick base pairing.

ii. If differences are determined to potentially impact method performance, it may be possible to perform a product specific verification to support the platform qualification and validation by assessing only the method attributes that would be most affected by the differences. For example, for gRNA purity assays, confirming that method accuracy and precision are not affected by different gRNA sequences may be sufficient.

c. For ex-vivo gene edited cell-based gene therapy products (ex vivo GE products), platform analytical procedures may include standardized flow cytometry panels for identity and purity testing, potency assays based on mechanism of action, and safety testing protocols for genetic stability (e.g., karyotyping or chromosomal aberration detection protocols). For example, validated flow cytometry marker panels identifying critical cell surface markers can serve as a scientific foundation for identity method selection across similar cell types. You may consider leveraging non-proprietary public knowledge to support the use of analytical methods that have been validated in scientific literature, performing bridging studies as needed to confirm suitability for their specific product and manufacturing context.

2. Lot release specifications[14]

a. It may be scientifically appropriate to leverage prior knowledge to support a lot release specification, depending on the similarity(s) of the GE component or product structure and the manufacturing process. Prior knowledge may be included as part of the justification of specifications section.

i. Prior knowledge may be considered for justifying which quality attributes to include in a lot release specification and suitable acceptance criteria for those quality attributes. For example, a gRNA with a similar size, structure, manufacturing processes, and formulation, but a different spacer sequence, may include the same attributes, use the same methods, and have the same acceptance criteria in a lot release specification as other gRNAs that are part of the same platform.

ii. The need to include or exclude process residual testing in the release specification may be justified using data from similar

[14] A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.

components or products with a platform manufacturing process. For example, not testing a cell-based GE product for the persistence of the ribonucleoprotein components may be justified with prior knowledge of ribonucleoprotein clearance (half-life) during culture for similar products.

iii. Although you may be able to leverage some information for identity and potency, such as the analytical method, testing for these attributes is intended to be product specific. Additional considerations or justification may be necessary to leverage prior knowledge for these product dependent attributes.

iv. For ex vivo GE products, lot release specifications may leverage prior knowledge regarding Critical Quality Attributes (CQAs) such as identity markers, purity specifications, potency assays, and safety parameters. You may reference established CQA definitions derived from collective experience to promote harmonization across the field. For example, standardized potency assay designs such as mechanism-of-action based assays, or cytotoxicity assays for CAR-T cells may be considered for leveraging across similar products within the same therapeutic class.

3. Stability data

a. The scientific appropriateness of leveraging stability data for similar components or products may depend on the manufacturing process, composition and formulation, container closure, storage condition, and the stage of product development.

i. Stability data from similar components or products may be considered for leveraging to support initiation of early phase clinical studies to justify stability of the component or product over the duration of the planned clinical trial. 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.

ii. For ex vivo GE products stability data in early phase studies, including cryopreservation protocols, critical reagents and post-thaw recovery procedures may be derived from a sponsor's own prior experience with similar products, third-party master files with appropriate authorization, public knowledge, or collaborative data-sharing initiatives. For example, prior knowledge on DMSO concentrations, controlled-rate freezing protocols, and alternative

cryoprotectants may be considered for leveraging in INDs to establish stability protocols for new products. Sponsors may also consider leveraging non-proprietary, publicly available CMC data to inform and justify their selection of cell culture media, cytokine supplements, or cryoprotectants by referencing existing scientific literature, pharmacopeial monographs, and databases. For example, USP General Chapter <1044> Cryopreservation of Cells includes information on optimal cell harvesting phase, storage conditions and labeling requirements.

iii. Prior knowledge of stability may be considered to support a commercial shelf life in addition to real time stability data of primary product lots. However, prior knowledge is not intended to replace long-term, real-time product stability data in a BLA submission. Additionally, flexibility may be given for critical components for manufacture of ex vivo GE products.

iv. In appropriate circumstances, data demonstrating stability of the product (such as adsorption and activity) in the delivery device may be considered for leveraging from a related product, provided there is similarity in the products (e.g., same class and formulation), device (for example, intended use, regulatory status, performance), and delivery process (like route of administration and flow rate). We note that administration of cell and gene therapy products may involve the use of sophisticated delivery devices and, in some instances, raise issues of comparability and device compatibility. For studies requiring use of delivery devices, we encourage early interaction with the respective division for feedback on data submission requirements and labelling considerations.

b. Prior knowledge on the stability of components or products may be considered to justify the establishment of a stability protocol for a new product or component in the platform.

i. This may include an understanding of which quality attributes are important to monitor for stability, appropriate methods, and acceptance criteria to include in the stability specification, predicting trends in stability data, and the appropriate stressed or accelerated testing conditions.

4. Comparability data

a. Comparability data obtained using one GE component or product may be considered to support implementation of similar changes in other

components/products using the same GE product platform(s). Such platform data may be considered to facilitate a risk assessment of the changes to product quality and inform analytical comparability study design.

i. When leveraging comparability data from a GE component or product, the impact of product differences on a comparability determination should be assessed for each relevant quality attribute. For example, the impact of manufacturing changes on product potency may need to be evaluated on a product-specific basis for products with different editing target genes.

ii. Depending on the similarity in molecular structure and manufacturing process, platform comparability data from representative GE components or products may be sufficient to support changes in other components or products across the platform or justify a reduced set of quality attributes to be measured. For example, data supporting a reagent change for one gRNA may be considered to support the same reagent change when manufacturing other gRNAs of a similar structure.

5. Process characterization and process validation data

a. Process characterization data may be considered for leveraging between products or components that use the same platform manufacturing process to determine criticality of process parameters, define proven acceptable ranges of these parameters, and to develop overall microbial control and potency assurance strategies.

b. For ex vivo GE products, process characterization data may be considered for leveraging across products that use similar starting materials, culture media, and expansion protocols. Platform manufacturing processes may include standardized procedures for cell isolation and purification, scale-up strategies from laboratory flasks to bioreactors, and automation technologies such as closed-system bioreactors and integrated platforms. Process control parameters such as temperature, pH, dissolved oxygen, cell density, and passage number limits established for one product may inform similar products within the same platform.

c. Data from platform manufacturing process development studies may be considered to support the duration of in-process material hold times between similar products.

d. Process performance qualification (PPQ) study data from a GE component or product may be considered for leveraging to support manufacturing process validation of multiple GE components or products that use the same manufacturing process platform at the same manufacturing site.

Platform process validation data may be considered to inform a new PPQ study design such as determination of the number of PPQ runs needed and sampling strategies. In many cases, with the use of supportive platform PPQ data, a reduced number of PPQ batches may be justified.

e. The extent of support from the leveraged data depends on similarities between products and manufacturing processes. Factors to consider when attempting to leverage data include the following:

i. Effect of different editing outcomes on process parameters and product CQAs of ex vivo GE products.

ii. Difference in product or component strength.

iii. GE-independent features of the manufacturing process such as the starting cell material for ex vivo GE products compositions of LNPs for in vivo GE products, purification process for vectors, manufacturing scale, facility design and equipment.

6. Manufacturing Facilities

For manufacturing facilities, prior knowledge may be considered for leveraging for cleanroom classification requirements, environmental monitoring programs, HVAC system design, and contamination control strategies. Standardized equipment qualification procedures, including installation, operational, and performance qualification (IQ/OQ/PQ) steps, may be referenced from established regulatory guidance and industry standards. Environmental monitoring data for classified GMP production spaces may be shared to establish common industry standards for alert and action limits.

## B. Nonclinical

The scope of nonclinical data needed to support investigational GE products is dependent on the properties, components, and benefit-risk determination for each product. Therefore, a stepwise approach to the nonclinical testing program is recommended where existing knowledge regarding the product and proposed indication should inform the nonclinical program, including kind, duration, and scope of nonclinical testing needed to enter into a clinical trial. The nonclinical program for a product may include leveraging of data to support the rationale and safety for the administration of the investigational product in the proposed clinical trial, as appropriate. Examples of leveraged data that may be considered include the following: a) in vitro studies b) in silico studies, c) other new approach methodologies (NAMs), d) in vivo studies using an analogous animal product, and e) nonclinical data from studies evaluating a relevant product for another indication. The sponsor should integrate data from all available sources to establish adequate scientific justification and safety to support initiation of the proposed clinical trial. When nonclinical data from other relevant product(s) is leveraged to support the

rationale and safety for administration of an investigational GE product, detailed information on the similarities and differences (e.g., manufacturing process, final formulation, key lot release specifications etc.) between the intended product and the product(s) being leveraged should be included. If it is determined that particular aspects of a nonclinical testing program for a GE product may be leveraged to limit or refine further nonclinical testing, a comprehensive justification with supporting data for why additional nonclinical evaluation is unnecessary should be provided and discussed with FDA at the early stages of development (e.g., pre-IND).

The overall objectives of a nonclinical program for a human GE product are generally the same as for other gene therapy products, as described in FDA's Guidance for Industry: "Preclinical Assessment of Investigational Cellular and Gene Therapy Products" November 2013 ("Preclinical Assessment Guidance").[15] These objectives include: 1) identification of a pharmacologically-active dose level range; 2) recommendations for an initial clinical dose level, dose-escalation scheme, and dosing regimen; 3) establishment of feasibility and reasonable safety of the proposed clinical route of administration (ROA); 4) support for the target patient population(s); and 5) identification of potential toxicities and physiologic parameters that help guide clinical monitoring and risk mitigation plans.

1. Leveraging Knowledge Based on Product Type

The scope of nonclinical data needed to support an investigational GE product is dependent on the properties, components, and potential benefit-risks associated with each individual product. The following general elements may be considered when leveraging nonclinical data across different ex vivo GE products and in vivo GE products.

a. Ex vivo GE products

i. Data regarding the biological activity associated with specific genomic edits may be considered for leveraging between products that contain the same on-target genomic edits (e.g., gain or loss of activity resulting from knockout or knock-in of a specific gene or differentiation capacity of progenitor cells) using the same editor. The biological activity of each editor and gRNA combination should be assessed.

ii. Product attributes independent of the GE component may be considered for leveraging across products. For example, safety and activity data related to the specificity and affinity/avidity of the binding domain of a genome edited CAR T cell product may be

[15] FDA Guidance for Industry Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013), available at Preclinical Assessment of Investigational Cellular and Gene Therapy Products | FDA

considered for leveraging, provided that the single-chain variable fragment (scFv) component of the targeting domain and cell type are identical.

b. In vivo GE products

In general, the scientific appropriateness of leveraging nonclinical information across in vivo GE products will depend on the similarities between the products (e.g., editor, vector), manufacturing process, final formulation (e.g., LNP composition and molar ratios), empty/full vector capsid, ROA, dose levels and dosing regimen.

i. Proof-of-concept data demonstrating editing and biological activity in a single animal model of a monogenic disease may be considered for leveraging to understand the feasibility of editing, demonstrate the predicted biological response consistent with the intended mechanism of action, and to support the scientific rationale for the proposed product. However, studies should be conducted for each editor and gRNA combination to evaluate the in vitro on-target editing efficiency and corresponding biological activity in relevant human cells expressing the clinical target mutation.

ii. The overall objectives for nonclinical biodistribution (BD) studies are outlined in the ICH S12 Guideline. BD data may be considered for leveraging across nonclinical developmental programs, with consideration given to whether the delivery vectors are sufficiently similar and any differences between leveraged products are not expected to impact the BD profiles. For example, BD data for LNPs may be considered for leveraging across products if the LNP's physiochemical properties (i.e., lipid identity, ratio, polydispersity index, zeta potential, etc.) are similar, and the differences in encapsulated material ('cargo') between products are not expected to impact the LNP's physiochemical characteristics, such as nanoparticle size, which can impact organ or tissue distribution. For viral vectors, BD data may be considered for leveraging across products if a similar vector capsid is used and any differences in expression cassette (e.g., regulatory elements, transgene, promoter, and any other functional elements) between the vector products are not anticipated to significantly impact the gene expression profile. To leverage BD data for GE products using viral delivery, the manufacturing process and properties such as vector titer, empty/full capsid ratio, post-translational modifications, vector genome methylation, etc., in addition to the titer assays used, should also be similar. Leveraged

BD data may be considered for identifying representative human tissues/cell types that should be assessed further for on- and off-target editing by the GE components for each product. Comprehensive archiving of all tissues should be conducted for in vivo BD studies for possible future assessment.

iii. Provided that the BD profile and product characteristics highlighted in (1)(b)(ii) are sufficiently similar, general toxicology data dependent on the product's attributes and independent of the editing components, such as the delivery vector, may be considered for leveraging between products. Additional studies should be focused on assessing the safety of the cargo and resulting editing activity of each gRNA. For LNPs, genotoxicity assessments (e.g., in vitro micronucleus test, *in vitro* mammalian cell hypoxanthine-guanine phosphoribosyltransferase [HPRT] gene mutation test, etc.) may be considered for leveraging. BD data indicating no distribution to the gonads may be considered for leveraging to forgo developmental and reproductive toxicities (DART) and germline transmission studies for a product with a similar delivery vector. The potential for leveraging DART or germline transmission data when editing is observed in the gonads should be discussed with the FDA.

c. Other Considerations

i. DART: For certain GE products, standard DART studies outlined in ICH S5(R3) may not be appropriate given potential differences in product pharmacokinetic profiles, biological activity, and limited relevance of nonclinical animal models. A risk-based approach that evaluates target tissue expression in reproductive organs and BD patterns should be considered when leveraging DART data. Early engagement with the FDA on DART requirements and leveraging data is recommended to avoid unnecessary delays in product development.

ii. Genotoxicity: Genotoxicity data may be considered for leveraging across GE products when the components and formulations are sufficiently similar and not expected to alter the genotoxic profile. Sponsors should follow the principles outlined in ICH S2(R1) when assessing the scientific rationale for leveraging genotoxicity data.

1. For LNP-formulated products, genotoxicity studies may be considered for leveraging for subsequent products when all lipid components, including ionizable lipids, cholesterol,

and PEG-lipids, are identical in type and ratio. LNP components, purification, and formulation processes should be substantially similar, ensuring comparable particle characteristics and impurity profiles. The cargo should not alter LNP physicochemical properties (i.e., size, charge, stability) or introduce additional genotoxic concerns. Changes in cargo (i.e., sequence, length, chemical modifications) should be evaluated for their potential impact on LNP behavior and genotoxic risk. Manufacturing-related impurities should be comparable between products, particularly those with known or potential genotoxic properties.

2. Data leveraging may not be appropriate when novel components or manufacturing processes are introduced, and when significant changes in impurity profiles or levels occur. Sponsors are encouraged to engage in early dialogue with FDA to discuss the appropriateness of leveraging existing genotoxicity data for their nonclinical development program.

iii. Transgene: Even with an identical vector backbone and expression cassette, fundamental differences in transgene expression and functionality can make it challenging to leverage biological activity and safety data between different transgenes. Each transgene may have a unique expression pattern and safety profile depending on transgene-specific properties. Codon optimization strategies may result in distinct expression and toxicity profiles in both on-target and off-target tissues. Furthermore, any integrated selection markers, purification tags, or reporter genes fused to the original transgene may potentially impact the new transgene's intended function. These factors should be addressed when leveraging data and developing the nonclinical program.

d. Clinical Experience

i In some cases, clinical data may be available from relevant products that can help to inform certain safety risks and dose level selection for the proposed clinical trial. If existing clinical data is used to help support safety and dose level selection, a discussion should be provided on: a) the similarities and differences between the intended product and the other relevant products demonstrating sufficient similarity, b) ROA, and c) dose levels and dosing regimen evaluated in the previous clinical studies compared to the proposed clinical trial.

ii. In lieu of nonclinical studies in juvenile animals, leveraging clinical data from adult patients may be applicable for determining pediatric starting dose levels, and we recommend that the sponsor addresses prospect of direct benefit and scientifically justifies dose extrapolation from adult data based on similar disease characteristics and exposure-response relationships between adult and pediatric populations. Sponsors are encouraged to engage in early dialogue with FDA to discuss the appropriateness of leveraging this existing data for their nonclinical development program.

2. Leveraging Bioinformatics Knowledge

Off-target analysis and genomic integrity assessment of all GE products relying on next-generation sequencing (NGS) methods and bioinformatics analysis tools are essential for assessing drug product safety. Off-target and genomic integrity data is recommended to assess the safety of each drug product[16] targeting a specific site in the genome, but this data may be considered for leveraging in some circumstances. However, leveraging certain bioinformatics information such as study design(s), methods, analysis tools, and sequencing technologies may be more broadly appropriate across multiple types of GE products. Specific considerations and examples are provided below.

a. Off-target assessment strategies and assay parameters

i. Off-target assessment strategies may be considered for leveraging across different GE products that use editors with an identical mechanism of action. Specifically, a specific set of methods for the nomination and confirmation of off-target sites for one drug product may be considered for leveraging for a similar safety assessment of other drug products. Similarly, a genomic integrity analysis method(s) used for one drug product may be leveraging for a similar assessment of other drug products.

ii. When the intended on-target edit rates achieved by different drug products are similar, the assay parameters may be considered for leveraging. Specific assay parameters include, but are not limited to: the amount of starting material, concentrations of GE components, culture methods (where applicable), and use of appropriate controls.

[16] 21 CFR 601.2.

b. Next generation sequencing methods

i. For nonclinical programs that rely on using predetermined sets of off-target and genomic integrity assays (see section B.2.a.i), a specific NGS strategy may be considered for leveraging.

For example, a specific NGS-based confirmatory testing method that was implemented at a certain sequencing depth and with specific sequence quality acceptance criteria for one drug product may be considered for leveraging to perform a similar assessment of other drug products. Similarly, NGS methods may be considered for leveraging for acquiring sequencing data during off-target nomination, for on-target assessment, and for NGS-based chromosomal integrity analysis.

c. Analysis methods and pipelines

i. The NGS data acquired from genome edited samples can be assessed using a specific set of bioinformatics tools or pipeline(s). A bioinformatics pipeline may include several bioinformatics tools that are implemented in a specific order. For example, NGS data generated from a specific off-target assay may be analyzed using a bioinformatics pipeline specifically developed to analyze such data. Bioinformatics pipelines may be considered for leveraging to analyze similar data obtained from different GE products that were assessed with the same off-target assay. However, specific parameters such as target sequence and mismatch parameters (if applicable) may need to be modified when applying such pipelines to analyze NGS data obtained from different drug products. For example, a GUIDE-seq analysis pipeline implemented for two GE products will differ in the input target sequence if the drug products target distinct regions in the genome.

ii. In lieu of using bioinformatics pipeline(s), sponsors may use a specific tool to perform a specific step of NGS data analysis. Some of these bioinformatics tools may have general utility in analyzing NGS data from different sources (e.g., DNA sequence, RNA sequence, etc.). For example, bioinformatics tools for either sequence quality assessment, or sequence trimming, or sequence alignment have broad utility and may be considered for leveraging to analyze different types of NGS data obtained from testing different GE drug products.

iii. Sponsors may also choose to leverage sequencing depth/quality metrics and/or sequence alignment metrics, or other parameters, as

applicable, when querying the quality of the NGS data or when setting up the acceptance criteria for NGS data obtained from testing different GE products.

d. Leveraging off-target data

i. The sequence recognition component or gRNA sequence is one of the main determinants of off-target editing risk in any genome editing modality. If a proposed drug product uses a gRNA and a genome editor in a specific cell type that is identical to ones used in another clinical program, off-target data for that gRNA may be considered for leveraging. For example, off-target data may be considered for leveraging between ex vivo genome edited cell-based gene therapy products (ex vivo GE products) harboring identical genome edits.

ii. Data obtained from genomic integrity studies may also be considered for leveraging if drug products use an identical gRNA sequence(s) and gene editor in a specific cell type. However, under certain circumstances, additional genomic integrity assessment may be needed if the genome edits are intended in patient cells that are known to have altered DNA repair machinery/processes due to an underlying disease. For example, additional studies to assess chromosomal integrity may be needed for drug products generated using patient cells that may have impaired cellular DNA repair processes.

iii. For drug products using an identical gRNA but different genome editors preferring common protospacer adjacent motif (PAM) sequences, computationally nominated off-target sites may be considered for leveraging. For example, data from computational or in silico off-target nomination studies may be considered for leveraging between two drug products using either Cas9 or base editors with an identical gRNA. In this case, a safety assessment of computationally nominated sites may be limited to performing confirmatory testing in samples edited using the intended editor. However, additional testing for off-target editing that is specific to the genome editor may be needed.

e. Leveraging bioinformatics data may not be appropriate when the data are product-specific due to the sequence-specific nature of genome editing:

i. It is generally not scientifically appropriate to leverage off-target assessment data across products using different guide RNAs or sequence recognition components.[17, 18]

ii. On-target editing outcome data is specific to each genomic locus and is generally not scientifically appropriate for directly transferring between products targeting different sites, even when using identical editing mechanisms.[19, 20]

iii. Genomic integrity assessment results are influenced by on-target and off-target editing activity, and this data is generally not scientifically appropriate for leveraging if drug products edit different genomic locations.

## C. Clinical

Sponsors planning to leverage clinical data or general prior knowledge are encouraged to engage with FDA in the early stages of product development through available opportunities such as INTERACT (**IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER/CDER Produc**T**s) or pre-IND meetings. When assessing whether to leverage clinical data within a clinical development program utilizing one or more platform technology attributes, or across such clinical development programs, sponsors should consider how the characteristics of the platform technology may impact the clinical evaluation of the product. Sponsors should determine if leveraging of prior information and/or data is intended to inform one or more aspects of the proposed study, such as the design, conduct, and/or analysis to support a future licensing application.

1. Leveraging prior clinical data and information for *trial design:*

   a. A sponsor may plan to leverage data/results from prior clinical experience to inform aspects of the design of a clinical trial, including the dose limiting toxicity (DLT) definitions, monitoring intervals and duration of monitoring, dose selection, based on the experience in prior clinical studies. Other aspects of the clinical trial design such as the appropriateness of re-dosing, exposure-response evaluation, the type and timing of the assessment of biomarkers and/or clinical outcome assessments, in other trials may also inform the trial design.

   b. A Sponsor may also consider leveraging the clinical pharmacology assessment of prior trials to inform assessments such as biodistribution, vector shedding, drug-drug interactions, immunogenicity, etc.

[17] 21 CFR 312.23(a)(7) and 21 CFR 312.23(a)(8)
[18] 21 CFR 601.2.
[19] 21 CFR 312.23(a)(7) and 21 CFR 312.23(a)(8)
[20] 21 CFR 601.2.

2. Leveraging prior clinical data and information *to inform trial conduct or analysis*

   a. A sponsor may consider leveraging clinical data already collected, for the purpose of abbreviating the safety database, efficacy database, PK database, DDI liability, as appropriate based on whether there are expected clinical differences. Such expected clinical differences may be based on patient population factors (e.g., disease setting, prior therapies, concomitant medications) or product related characteristics (product comparability, route of administration and frequency of dosing, etc.) that are clinically relevant. The prior data and information that is leveraged in this way, may be included in integrated assessments for safety and efficacy, as appropriate.

3. Leveraging data from *Natural History Studies and RWE*

   a. Sponsors should refer to FDA guidances on Natural History Studies[21] and RWE.[22, 23]. Sponsors planning to use natural history studies and real-world data to support future licensure are encouraged to submit a proposal early in product development, to ensure the data is fit for purpose. External stakeholders are encouraged to create shared databases that may be considered for supporting the development of products across multiple sponsors.

4. Leveraging data for *long-term follow-up studies*

   a. Sponsors should refer to current guidance on long-term follow-up specific to the type of therapy. The FDA remains open to reconsider the type of data collected, frequency and duration of follow up monitoring based on the cumulative safety data and any emergence of new safety signals to reduce unnecessary burden on the patients and the Sponsors. Sponsors are encouraged to discuss long-term monitoring plans with appropriate justification throughout product development.

[21] FDA Draft Guidance for Industry, Rare Diseases Natural History Studies for Drug Development (March 2019), available at **Rare Diseases: Natural History Studies for Drug Development**

[22] FDA Guidance for Industry, Considerations or the Use of Real-Word Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (August 2023), available at **Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products**

[23] FDA Guidance for Industry, Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products (September 2022), available at **Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products**

## IV. HOW TO SUBMIT INFORMATION FOR PROPOSED LEVERAGING

During clinical development, a sponsor may leverage (1) applicable public knowledge or (2) platform knowledge.

- To leverage public knowledge, the referenced material (e.g., publication) should be provided in the submission and should be sufficiently granular and provide adequate information on the subject matter of the study, for FDA to evaluate if it is applicable.

- When using publicly available data, sponsors should,

    - Provide a summary of literature sources, including its relevance to their product,
    - Justify that the referenced data are applicable to their specific cell type, source, and intended use, and
    - Supply bridging or confirmatory data as appropriate

- Platform information and data may be provided directly in the IND submission, or it may be referenced to a previously submitted IND or a Master File (MF).[24] MFs can contain manufacturing and analytical method information as well as nonclinical testing information/data from sponsors or contract manufacturing and testing organizations. If the file being referenced has been submitted by someone other than the sponsor, a written statement of authorization to reference the platform information/data must be provided (21 CFR 312.23(b)).

- When you are studying multiple versions of a GE based product in an early-phase clinical trial for a single disease, you may cross-reference the primary IND for CMC, P/T and/or clinical information.[25]

- Regardless of whether the platform information and data are being provided directly in the IND submission or is cross-referenced, the justification for why the knowledge is applicable to the current product should be provided in the IND for that product.

For a biologics license application (BLA), while information and data about certain materials such as excipients can be cross-referenced with proper authorization, BLAs may not incorporate by reference information or data that applies to drug substances, drug substance intermediates, and drug products, as this information must be contained in the BLA (21 CFR 601.2(a); 21 CFR 601.2(g)). However, such information may still be considered for leveraging – including if generated by a third party – if it is provided directly in the BLA (21 CFR 601.2). FDA requires an applicant to submit information about drug substances, drug substance intermediates, and

[24] For additional information please refer to the FDA Draft Guidance for Industry "Drug Master Files" (October 2019); available at Drug Master Files Guidance for Industry | FDA. When final, this guidance will represent the FDA's current thinking on this topic.

[25] For additional guidance, please refer to the FDA Guidance for Industry "Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial" (November 2022); available at Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial.

drug products directly to the BLA because, at the time a BLA is submitted, FDA expects the sponsor to have knowledge of and direct control over the manufacturing process.

If a sponsor is interested in leveraging prior knowledge in the development of a product, we recommend that they discuss this with FDA as early as possible in the product development lifecycle (e.g., INTERACT and pre-IND meetings) to avoid any issues later in development.[26]

Table 1. Examples of Types of Data and Other Information that May be Considered for Leveraging

| | Gene Editing (general) | Ex vivo GE products |
|---|---|---|
| Analytical methods | For gRNA purity assays, confirming that method accuracy and precision are not affected by different gRNA sequences may be sufficient. | Standardized flow cytometry panels for identity and purity testing across similar cell types; validated potency assays based on mechanism of action (e.g., cytotoxicity assays for CAR-T cells, etc.); established safety testing protocols for sterility and mycoplasma. |
| Lot Release Specification | gRNA with a similar size, structure, manufacturing processes, and formulation, but a different spacer sequence, may include the same attributes use the same methods, and have the same acceptance criteria in a lot release specification as other gRNAs that are part of the same platform. | Cell therapy products with similar starting materials and manufacturing processes may share CQAs including identity markers, purity specifications, and potency assays; standardized acceptance criteria for viability, cell count, and functional activity across platform products. |

[26] For additional guidance please refer to the FDA Guidance for Industry "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products" September 2023; available at Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products | FDA.

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|---|---|---|
| Stability data | To help support 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. | |
| Comparability data | Data supporting a reagent change for one gRNA to support the same reagent change when manufacturing other gRNAs of a similar structure. | Manufacturing process changes such as media optimization or scale-up strategies; equipment changes for similar cell expansion platforms; facility transfers for products using comparable manufacturing processes. |
| Cell Banking | Cell banking strategies, including Master and Working Cell Bank approaches for allogeneic products and cellular stock approaches for autologous therapies, may also benefit from platform knowledge. For example, information on two-tiered cell banking approaches may be considered for leveraging from ICH Q5D: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products or USP General Chapter <1042> Cell Banking Practices for Recombinant Biologics; Draft Guidance for Industry: Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products. April 2024. | |
| Process Characterization | | Cell isolation and purification methods; culture media optimization and serum-free formulations; process control parameters (temperature, pH, dissolved oxygen, passage limits); |

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|---|---|---|
| | | automation platform validation data. |
| Manufacturing facilities | Cleanroom classification and environmental monitoring; equipment qualification (IQ/OQ/PQ) for cell processing equipment; contamination control strategies; facility design standards for cell therapy manufacturing | |

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