Considerations for Leveraging Prior Knowledge for Cell and Gene Therapy Products

CASSS 2026

Stella S. Lee, PhD
Gene Therapy Branch 4
Division of Gene Therapy 2
Office of Gene Therapy
Office of Therapeutic Products
CBER, FDA

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

Draft Guidance for Industry

Docket No. FDA-2026-D-1257

Outline

- **Why** consider leveraging prior knowledge?
- **To whom** does leveraging prior knowledge apply?
- **When** to consider leveraging prior knowledge?
- **What** is considered prior knowledge, and what information can be leveraged?
- **How** to submit prior knowledge information?

Why consider leveraging prior knowledge?

- Development of cell and gene therapy (CGT) products presents unique scientific and regulatory challenges
- The amount of prior knowledge available to support multiple aspects of CGT product development increases as more CGT products are developed
- Data leveraging can expedite product development by streamlining regulatory submissions
- Can be particularly helpful for products intended to treat rare, serious or life-threatening diseases

To whom does leveraging prior knowledge apply?

- Cell and gene therapy products, including those incorporating genome editing (GE)
- The ability to leverage data **does not require an approved product**
  - Depends on **similarities** in product/component design, cell source, manufacturing process, final formulation, key quality attributes, etc.
  - If differences exist, the **degree of differences** determines the extent to which prior knowledge can be leveraged from full datasets to partial information with supplementation

When to consider leveraging prior knowledge?

- Throughout a product's lifecycle
  - Data may be leveraged in investigational new drug applications (INDs) and biologic license applications (BLAs)
- Encourage sponsors to discuss data leveraging opportunities with FDA as early as possible in product development (e.g., INTERACT and pre-IND meetings)

What is considered prior knowledge?

- **Public knowledge**
  - Scientific information based on widely accepted scientific principles that are typically long-standing
- **Platform knowledge***
  - Well-understood and reproducible technology(s) applied to the development of a product that consists of the same or highly similar features across development programs
  - Sponsor's own data from previous products using the same or similar manufacturing platforms
  - Third-party platform knowledge

The term **platform as used here differs from the use of the terms "platform technology" or "designated platform technology" as defined under FDA's Platform Technology Designation Program*

What information can be leveraged?

CMC

- Process characterization/ validation data
- Lot release specification
- Analytical methods & method qualification/ validation data
- Comparability data
- Stability data

Nonclinical

- Proof of concept (POC) data
- Safety data (e.g., immunogenicity, toxicity)
- Biodistribution data

Bioinformatics

- Bioinformatics methods & analysis tools

Clinical

- Previous clinical experience

and more…

What information can be leveraged for CMC?

- Process characterization/ validation data
- Lot release specification
- Analytical methods & method qualification/ validation data
- Comparability data
- Stability data

•Process characterization data between products/components using the same platform manufacturing process to determine process parameter criticality, define proven acceptable ranges of these parameters, etc.

•Process performance qualification (PPQ) data from one product/component may be used to inform a new PPQ study design (e.g., number of PPQ runs needed) and/or support process validation for a similar product using the same manufacturing process at the same manufacturing site

- e.g., PPQ study from one GE product may support process validation of other product "variants" incorporating different gRNAs targeting different mutations in a single gene

What information can be leveraged for CMC?

- Process characterization/ validation data
- Lot release specification
- Analytical methods & method qualification/ validation data
- Comparability data
- Stability data

•Justify which quality attributes to include in a lot release specification and suitable acceptance criteria for those quality attributes

- e.g., gRNAs with a similar size/structure, same manufacturing process and formulation, but different spacer sequences, may use the same lot release specification (same test methods and acceptance criteria)

•Justify the need to include or exclude process-related residual testing using data from similar products/components with a platform manufacturing process

- e.g., testing residual ribonucleoprotein components for a cell-based GE product may be excluded from the release specification with prior ribonucleoprotein clearance data during culture for similar products

Additional considerations or justification may be necessary to leverage prior knowledge for product-specific attributes

What information can be leveraged for CMC?

- Process characterization/ validation data
- Lot release specification
- Analytical methods & method qualification/ validation data
- Comparability data
- Stability data

•Qualification/validation data of a platform analytical method, as defined in ICH Q2(R2), may be applied across similar components/products, depending on similarities between test articles

If differences potentially impact method performance, product-specific verification may be needed

- *e.g., gRNA purity assays: verifying that method accuracy and precision are not affected by different gRNA sequences*

What information can be leveraged for CMC?

- Process characterization/ validation data
- Lot release specification
- Analytical methods & method qualification/ validation data
- Comparability data
- Stability data

•Comparability data obtained from one product/component may support changes in other similar products/components

- e.g., data supporting a reagent change for one gRNA may support the same reagent change when manufacturing other gRNAs with similar structure

What information can be leveraged for CMC?

- Process characterization/ validation data
- Lot release specification
- Analytical methods & method qualification/ validation data
- Comparability data
- Stability data

•Stability data from similar products may support initiation of early phase clinical studies to justify stability of a product/component over the duration of the planned clinical trial

  - e.g., stability data of an mRNA encoding one nuclease may support other mRNA components encoding a different nuclease, if stored in the same conditions and container closure

•Prior knowledge of stability may support commercial shelf life in addition to real time stability data of primary product lots

  - e.g., stability data from clinical lots, if the lots are representative, such as manufactured with the commercial process, using the commercial formulation and in the commercial container closure

•In-use stability and delivery device compatibility data for similar products that have the same formulation and are administered using the same delivery device

What information can be leveraged for nonclinical?

- Proof of concept (POC)
- Safety data (e.g., immunogenicity, toxicity)
- Biodistribution (BD) data

•Ex vivo GE products: product attributes independent of the GE component may be leveraged

- e.g., safety/activity data related to the specificity and affinity of the binding domain of a CAR T product may be considered for leveraging, when the single-chain variable fragment (scFv) component of the targeting domain and cell type are identical

•In vivo GE products: BD data may be leveraged if the the delivery vectors are sufficiently similar, the route of administration (ROA) is the same, and differences (if any) are not expected to impact the BD profiles

- e.g., BD data for viral vectors, if the same vector capsid is used
- e.g., BD/genotoxicity data for lipid nanoparticles (LNPs) across products, if the LNP's physiochemical properties are identical

For GE products, editing activity at the target site and off-target editing risk will need to be evaluated for each editor and gRNA combination

What information can be leveraged for bioinformatics?

Bioinformatics methods and analysis tools

- Off-target assessment strategies and assay parameters
  - -e.g., a specific set of methods for nomination and confirmation of off-target sites for one GE product may be leveraged for a similar safety assessment of other GE products using editors with an identical mechanism of action

Leveraging bioinformatics data may not be appropriate when the data are product-specific due to the sequence-specific nature of genome editing (e.g., different guide RNAs or sequence recognition components)

What information can be leveraged for clinical?

Previous clinical experience

- Prior clinical data to inform dose, dose escalation and frequency, and meaningful endpoints
- Use of natural history studies and real-world data

How to submit prior knowledge information?

- Provide justification for why the prior knowledge is applicable
- During IND stage of development,
  - Information can be provided directly in the submission, or it may be cross-referenced to a previously submitted IND or Master File (MF)
  - If the file being referenced has been submitted by someone other than the sponsor, a written statement of authorization to reference the information must be provided
- For a BLA,
  - While reference information that applies to drug substances, drug substance intermediates, and drug products may be leveraged, it must be submitted directly in the BLA (per 21 CFR 601.2)

Summary

- Both public and platform knowledge can be leveraged to streamline CGT product development and regulatory submissions throughout the product lifecycle
- May be widely available or proprietary, requiring right of reference
- Ability to leverage depends on similarities in the structure of a product or component, manufacturing process, final formulation, etc.
- Applies to all disciplines (CMC, nonclinical, bioinformatics, and clinical)
- Early engagement with FDA is strongly recommended

Additional guidance documents

- Draft Guidance for Industry "**Considerations for the use of Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause**" from February 2026: Docket No. FDA-2026-D-1256
- Draft Guidance for Industry "**Safety Assessment of Genome Editing in Human Gene Therapy Products Using Next-Generation Sequencing**" from April 2026: Docket No. FDA-2026-D-1255
- Guidance for Industry "**Chemistry, Manufacturing, and Control Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application**" from May 2026

Contact Information

- **Stella S. Lee**
  stella.lee@fda.hhs.gov

- **Regulatory Questions: OTP Main Line – 240 402 8190**
  Email: OTPRPMS@fda.hhs.gov and Lori.Tull@fda.hhs.gov

- **OTP Learn Webinar Series:**
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
  Phone: 1-800-835-4709 or 240-402-8010

- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.gov
- **Follow us on Twitter:** https://www.twitter.com/fdacber


FDA
U.S. FOOD & DRUG
ADMINISTRATION