

Individualized Human Genome Editing Products: Considerations for BLA Submission and Postapproval Management

Draft Guidance for Industry

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I. INTRODUCTION

Human genome editing (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.¹ GE is a type of gene therapy that relies on GE components² to edit DNA. When a monogenic disease³ is caused by gene variants that differ among patients – including rare gene variants that are unique to a patient or shared by only a few patients – the GE components can be tailored to target each patient’s specific pathogenic gene variant. An individualized GE product⁴ can be designed to include multiple product variants,⁵ each tailored to target a specific pathogenic gene variant in the gene of interest.

This guidance is intended for sponsors and applicants developing individualized GE products. It addresses how an individualized GE product that includes multiple product variants can be submitted in a single Biologics License Application (BLA) under section 351(a) of the PHS

¹ See Guidance for Industry: *Human Gene Therapy Products Incorporating Human Genome Editing*, January 2024, <https://www.fda.gov/media/156894/download>.

² For the purposes of this guidance, a **genome editing component** is defined as any material that is essential for the intended genomic modification, including those that may not appear in the final drug product. Genome editing 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.

³ For purposes of this guidance, a **monogenic disease** is a disease caused by a pathogenic gene variant in a single gene, also known as a single-gene disorder or Mendelian disorder. Note that different pathogenic gene variants in the same gene can sometimes cause clinically distinct diseases.

⁴ For the purposes of this guidance, an **individualized genome editing product** is defined as a product where the genome editing components are designed to have variable physical features that are matched to specific patients or patient subgroups to address patient-specific gene variants.

⁵ For the purposes of this guidance, a **product variant** is defined as a specific instance of an individualized GE product where one or more physical features have been deliberately selected or modified to target a gene variant. A product variant maintains the core design of the product and shares the same IND or BLA with other product variants.

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Act.⁶ It explains how to specify the extent of GE component variation in a BLA and how to add new product variants to the BLA after licensure. This guidance also addresses related topics, including *in vitro* safety and potency evaluation of product variants, manufacturing process validation, labeling and indication statements, and drug naming and identification.

Existing FDA guidances on GE products address IND-stage chemistry, manufacturing, and controls (CMC); nonclinical and clinical trial design; evidentiary standards for approval of individualized therapies; and leveraging of CMC, nonclinical, and clinical knowledge across GE programs.^{7,8,9} This guidance complements those previously issued guidances by providing advice on how to prepare and submit BLAs and BLA supplements for individualized GE products. This guidance will also be helpful to sponsors who intend to evaluate an individualized GE product that includes multiple product variants under a single IND.

The scope of this guidance is limited to individualized GE products that meet all of the following criteria: (1) the product is intended to prevent, treat, or cure a monogenic disease or condition (e.g., autosomal dominant, recessive, or X-linked); (2) the disease or condition is caused by known pathogenic gene variants (e.g., single nucleotide variants, insertions, or deletions); and (3) all product variants in the BLA are designed to achieve the same editing outcome (e.g., correcting a pathogenic gene variant to the wild-type DNA sequence, or selectively inactivating a pathogenic gain-of-function allele). However, some principles in this guidance may be applicable to other individualized GE products.

The scope of this guidance does not include the design or conduct of clinical studies (including postmarketing clinical studies) to generate evidence of safety and effectiveness that is adequate to support a BLA. However, FDA intends to issue further guidance on this topic. This guidance also does not address individualized products that are not GE products, GE products that are not individualized, or specific BLA approval pathways (accelerated vs. traditional).

⁶ See Guidance for Industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, December 2004, <https://www.fda.gov/media/72397/download> (“bundling guidance”), explaining what may be considered a separate marketing application and what may be bundled for purposes of the user fee provisions of the Federal Food, Drug, and Cosmetic Act. The current guidance pertains to products to prevent, treat, or cure diseases or conditions caused by rare gene variants and, therefore, likely to have orphan-drug designation and related exemption from user fees. However, the concepts presented in the bundling guidance with respect to when a new original BLA or supplement are warranted are still generally applicable to individualized GE products (e.g., separate original submission for a change in dosage form, route of administration, container size/configuration, strength, indication; supplement to an approved application for a new or modified indication).

⁷ See Guidance for Industry: *Human Gene Therapy Products Incorporating Human Genome Editing*, January 2024, <https://www.fda.gov/media/156894/download>.

⁸ See Draft Guidance for Industry *Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause*, February 2026, <https://www.fda.gov/media/191247/download>. When finalized, this guidance will represent FDA’s current thinking on this topic.

⁹ See Draft Guidance for Industry *Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Gene Editing*, June 2026, <https://www.fda.gov/media/192810/download>. When finalized, this guidance will represent FDA’s current thinking on this topic.

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In general, FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the 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 guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

GE technologies offer a transformative approach to addressing monogenic diseases by directly targeting pathogenic gene variants at the DNA level. Although there are numerous types of GE technologies, individualized GE products often use a Cas-based editor that is directed to a specific location in the genome by a guide RNA (gRNA). After binding to DNA, the Cas-based editor enzymatically modifies or replaces the pathogenic DNA sequence, or introduces breaks that disrupt it. Editing can occur either inside the patient's body (using an *in vivo* product) or in cells that are removed from the patient, edited outside the body, and then returned to the patient (an *ex vivo* product).

In monogenic diseases, affected patients may have different pathogenic gene variants causing the disease. Individualized GE products address these gene variants using GE components whose roles differ depending on the product type. For *in vivo* products, the GE components comprise the active ingredients.¹⁰ For *ex vivo* products, the GE components are used during the manufacturing process to create the active ingredient (the edited cell).

Because a single product variant typically targets only one gene variant, a GE product intended to address a range of gene variants may include a set of modified GE components. The physical characteristics of these GE components that differ among product variants are termed variable features.¹¹ A BLA for an individualized GE product may therefore contain many product variants, each sharing the same core design and differing only in the GE components used to address each patient's specific gene variant. Defining the allowable limits of feature variation in the BLA serves two purposes: establishing the boundaries of the product and facilitating the post-licensure addition of new product variants that fall within those boundaries. Importantly, this framework provides a way for applicants to add new product variants to a BLA based on *in vitro* data without additional clinical studies.

¹⁰ **Active ingredient** means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect. (21 CFR 210.3(b)(7))

¹¹ For the purposes of this guidance, a **variable feature** is defined as a physical characteristic of a genome editing component that differs from lot to lot, within defined limits, to address specific gene variants.

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This guidance introduces the concept of the individualized feature space¹² (IFS), which describes the allowable limits of variation for the GE components of an individualized GE product. For example, for a GE product whose only variable feature is a gRNA spacer sequence, the IFS should describe which types of spacer sequences are allowable in the BLA – such as any spacer sequence that targets a defined class of pathogenic gene variants in a specified gene and results in the same editing outcome (e.g., correcting the gene so that it encodes the wild-type protein). A new product variant should be considered a manufacturing change for purposes of the BLA – rather than a new product – provided that: (1) the variable features of the product variant’s GE components fall within the established IFS; and (2) the resulting product variant is predicted to have adequate safety and activity based on clinical and/or *in vitro* data. Section III describes the IFS in detail and provides additional examples of how it applies to individualized GE products.

III. THE INDIVIDUALIZED FEATURE SPACE

The IFS describes the boundaries of the variable features of the GE components. Other aspects of the product should remain constant across all product variants, such as the strength, the formulation, the delivery vehicle or vector for *in vivo* products (e.g., lipid nanoparticle, viral capsid), and the specific cell type for *ex vivo* products.

Applicants should propose an IFS in the BLA that clearly delineates the boundaries of allowable variation for each variable feature of each GE component. Applicants may describe these boundaries using rules, menus of pre-specified options, or other appropriate means. For example, an applicant could propose a rule-based IFS for a gRNA spacer sequence and a menu-based IFS for an editor, as illustrated in **Table 1**. Importantly, the IFS should be supported by clinical data and coupled with explicit criteria for the *in vitro* safety and activity of the product variants. These criteria should include, for example, acceptable off-target editing and a minimum acceptance criterion for on-target editing (see Section V). Any product variant that does not meet these *in vitro* safety and activity criteria should not be included in the IFS.

All product variants included within a single BLA should share the same mechanism of action and intended editing outcome, thereby establishing a predictable connection between the product’s mechanism of action and the clinical safety and efficacy data from the product variants evaluated in clinical studies. For instance, base editors that have been modified to recognize different protospacer adjacent motif (PAM) sequences may be grouped within the same BLA, provided they share the same editing mechanism. Conversely, a GE product employing a fundamentally different mechanism (e.g., relying on a reverse transcriptase) should not be included in the same BLA as a base editor, because it would be a different product with distinct off-target and immunogenicity risks.

¹² For the purposes of this guidance, an *individualized feature space* (IFS) is defined as the allowable limits of variation for one or more variable features of a product’s genome editing components. An IFS includes only features or combinations of features known or predicted to have adequate safety and activity. Adding a new product variant within a pre-defined IFS should not be considered to result in a new product.

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FDA encourages sponsors to develop the IFS prospectively during their clinical development program, so that the clinical studies are designed to generate data that will support the proposed IFS boundaries. The clinical studies needed to support a proposed IFS will be highly case-specific. Relevant factors include the nature of the variable features, the breadth of the IFS boundaries, and the degree to which clinical evidence from the product variants evaluated in investigational studies can be extrapolated to unstudied product variants. FDA therefore encourages sponsors to discuss their proposed IFS and the clinical data needed to support it before initiating pivotal clinical studies.

Table 1: Example Individualized Feature Space for an Adenine Base Editor Genome Editing Product¹

Targeted Gene Variant in Gene X	gRNA ²	Editor ³
c.124C>T	gRNA-001	ABE-Cas9-A
c.456G>A	gRNA-002	ABE-Cas9-B
c.789G>A	gRNA-003	ABE-Cas9-A
c.999C>T	gRNA-004	ABE-Cas9-A
Other C>T or G>A gene variant in X ⁴	gRNA-###	ABE-Cas9-A or ABE-Cas9-B

¹This table illustrates the structure of an IFS, showing the allowable combinations of variable features. Each of the first four rows of the table represents a specific product variant; the last row represents the principle governing the addition of future product variants within the IFS. The *in vitro* safety and activity criteria that apply to product variants are not shown in this table and should be documented separately in the BLA.

²The gRNA in this example is a rule-based variable feature where the spacer sequence of each gRNA matches the gene variant being targeted.

³The editor in this example is a menu-based variable feature offering editor A or B that possess different PAM-recognition sites in the Cas9 domain, but a constant ABE domain. Each gRNA is exclusively paired with the editor demonstrated by *in vitro* data to have an acceptably high on-target editing efficiency and acceptably low off-target editing risk for the specific targeted gene variant.

⁴Additional gRNAs paired with either editor A or B can be added within the IFS if they meet specific criteria for *in vitro* safety and activity. This type of addition is an addition within the established IFS. In contrast, adding a new editor C to the menu of editor options in the IFS would be an IFS expansion.

To justify the proposed IFS boundaries, applicants should provide a robust scientific rationale supported primarily by clinical data from product variants evaluated in clinical studies, supplemented by *in vitro* data. The clinical data should also be used to establish the criteria for *in vitro* safety and activity that all product variants within the IFS should meet.

The proposed IFS in the initial BLA may list product variants that have not been evaluated in clinical studies, provided that (1) the product variants meet the criteria for *in vitro* safety and activity (see Section V); and (2) the clinical evidence from the product variants evaluated in clinical studies is deemed adequate to support the predicted safety and effectiveness of the product variants not evaluated in clinical studies. To meet this second condition, the clinical evidence should reflect the full range of product variants within the proposed IFS. Therefore, applicants should justify how the clinically evaluated product variants adequately span the entire

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proposed IFS. The acceptability of extrapolating safety and effectiveness data from approved product variants to additional product variants within the same monogenic disease will be a case-by-case determination based on considerations such as: (1) the extent of knowledge of the natural history of the disease, including genotype-phenotype associations; (2) factors affecting the safety or effectiveness of the product based on clinical studies, including the genotype (e.g., a severe gene variant causing no protein production that may lead to increased immunogenicity and higher safety risks); (3) potential remaining uncertainties regarding the clinical evidence supporting initial approval; and (4) the available scientific evidence supporting the relationship between *in vitro* and clinical data for the approved product variants.

A new product variant is not considered a new product – and adding it to the BLA does not change the established IFS – if its GE components fall within the boundaries of the IFS and the product variant meets the established *in vitro* safety and activity criteria. For instance, in the example shown in **Table 1**, a new gRNA-005 that targets a different gene variant within the same gene X could be incorporated into a new product variant within the IFS, provided that the new product variant meets the established *in vitro* safety and activity criteria.

In contrast, a new gRNA that does not meet the established *in vitro* safety and activity criteria should not be added to the BLA unless adequate additional clinical data is submitted to support the use of the product variant. Adding such a product variant involves amending the *in vitro* safety and activity criteria associated with the IFS, which should be supported by clinical data from investigational studies conducted with that specific product variant.

Altering the boundaries of an IFS to include previously unallowable product variants is considered an IFS expansion. The implications of an IFS expansion depend on the nature and risk profile of the proposed change, for example:

- **Adding a new editor protein with the same editing mechanism:** This constitutes an IFS expansion that adds a new menu item to the editors allowed in the IFS (see **Table 1**). Applicants should perform a comprehensive risk assessment – including *in vitro* safety and activity data for the new editor – to determine whether additional clinical evaluation is needed.
- **Adding a new editor that fundamentally changes the product’s mechanism or introduces significant new or unknown risks:** Product variants that use such an editor constitute a different product, and clinical data supporting the safety and effectiveness of the new product should be submitted in a new BLA rather than as a supplement to the existing BLA.

Detailed recommendations for adding new product variants to a BLA are provided in Section VI.

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IV. MANUFACTURING PROCESS AND CONTROL STRATEGY

A. Manufacturing Process Design and Control

During process design, applicants define the commercial manufacturing process based on knowledge gained through development and scale-up activities. For individualized GE products, the goal is to design a process capable of reliably manufacturing all current and future product variants that fall within the established IFS. In doing so, applicants should distinguish between the IFS, which describes the allowable variable features of the GE components, and the design space,¹³ which describes the allowable limits for input variables and process parameters in the manufacturing process.

Applicants should use process development studies and formal risk assessments¹⁴ to evaluate how the variable features of the GE components influence critical quality attributes and critical process parameters. To avoid the need to revalidate the manufacturing processes for each new GE component and product variant, the processes should be robust enough to accommodate variable features across the entire IFS. In particular, applicants should consider how GE components across the full range of the IFS might affect material attributes, manufacturing parameters, and product quality.

Manufacturing controls should be sufficiently robust to accommodate the full range of variable features within the IFS. Some of these controls will differ between *in vivo* and *ex vivo* products. For *in vivo* RNA-based products (where manufacturing control is primarily achieved through chemical/biochemical synthesis parameters), variations in RNA sequence length, GC content, or secondary structure may affect *in vitro* transcription yields or solid-phase synthesis efficiency. The process should be controlled to ensure consistent yield regardless of the specific sequence. Furthermore, changes to a gRNA spacer sequence may alter the impurity profile or chromatographic retention time, potentially requiring dynamic control of chromatography parameters (e.g., elution gradients) to ensure consistent removal of product-related impurities. For lipid nanoparticle products that contain RNA, if the length or secondary structure of the RNA varies, process controls around mixing rates, flow rates, and lipid-to-RNA ratios should be sufficiently robust to ensure consistent encapsulation efficiency and particle size.

For *ex vivo* products (where manufacturing control is primarily achieved through cell processing parameters), the editing efficiency will likely be affected by the variable

¹³ Design spaces are described in Guidance for Industry *Q8(R2) Pharmaceutical Development*, November 2009 <https://www.fda.gov/media/71535/download> and Guidance for Industry *Q11 Development and Manufacture of Drug Substances*, November 2012, <https://www.fda.gov/media/80909/download>. As defined in Q8(R2), a design space encompasses input variables and process parameters that have been demonstrated to provide assurance of quality, but certain changes would constitute moving out of the design space. A design space describes the conditions under which a product can be manufactured consistently to meet its expected quality attributes when there is variability or flexibility in starting materials or process parameters. In contrast, an IFS is a distinct type of space – an IFS describes the extent of allowable variation in the patient-specific variable features of the product’s GE components.

¹⁴ See Guidance for Industry *Q9(R1) Quality Risk Management*, May 2023, <https://www.fda.gov/media/167721/download>.

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features of the gRNAs and editors. Process controls surrounding cell processing, transfection, or electroporation may need to be carefully monitored or adjusted based on the specific GE components to ensure sufficient editing rates without causing excessive cellular toxicity. Other key considerations include the effect of specific GE components on cell viability or expansion parameters.

Applicants should establish specifications for the GE components, drug substance (DS),¹⁵ and drug product (DP)¹⁶ that are robust enough to cover all product variants within the IFS, yet sensitive enough to detect failures for specific product variants. These specifications form a critical part of the control strategy that allows information to be leveraged across product variants; a well-designed control strategy reduces the need for full characterization of new GE components and product variants.

In addition to activity and potency, which are addressed in Section V.A, two other aspects of the control strategy present unique considerations for individualized GE products:

- **Identity:** Identity testing confirms that the correct individualized DP is in the final container. Under 21 CFR 610.14, lot release identity tests must be performed on DP sampled from its final container after completion of labeling, and they must be adequate to distinguish the product from all other products being processed in the same facility. For *in vivo* individualized GE products, identity testing should include confirmation of the variable features of the GE components (e.g., sequencing to confirm the correct gRNA spacer sequence). For *ex vivo* products, identity testing should confirm the specific intended genomic edit in the cellular DP. In addition, manufacturers of *ex vivo* products should establish and document procedures for maintaining chain of identity (labeling and tracking) that link the cellular starting material collected from a specific patient to the DP manufactured from that material, at every stage of the manufacturing process.
- **Purity:** Under 21 CFR 610.13, biological products must be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved BLA. For individualized GE products, analytical methods used to detect product-related impurities in *in vivo* products (such as truncated RNAs) should be validated to demonstrate adequate performance across the range of the IFS, since the variable features of the GE components may affect the impurity profile of each product variant. For *ex vivo* products, in addition to controlling the

¹⁵ For the purposes of this guidance, the terms active ingredient and drug substance are used interchangeably.

¹⁶ Refers to those drug products that are biological products under 42 USC 262(i) and subject to licensure under section 351) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a) or (k)). See 42 U.S.C. 262(j). According to 42 USC 262(i), the term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

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purity of the GE components, DP purity control should include testing for residual GE components, unedited cells, and cell type analysis.

B. Manufacturing Process Validation

Expectations for manufacturing process validation apply to individualized GE products as they do for all other products.¹⁷ For individualized GE products, however, applicants should adapt the traditional process validation approach to accommodate product variability. At each stage, including process design, an applicant should address how variable features affect manufacturing performance. There are also considerable opportunities to leverage process validation information across product variants in an individualized GE product.

Process performance qualification (PPQ) studies should be designed based on a risk assessment, and PPQ for individualized GE products should account for how variable features and variable manufacturing conditions could affect process performance and product quality. If certain feature variations or manufacturing variables are identified as posing a high risk to product quality or process performance, then those aspects should be evaluated during the PPQ campaign. For example, batch size for an individualized GE product may range from large scale (for product variants intended for patients with relatively common gene variants) to small scale (for product variants intended for only one patient). For such a product that may be manufactured at different scales, PPQ studies should include representative runs that bracket the extremes of process scale. In general, however, if FDA determines that data from the process design stage is adequate to ensure process performance across all potential product variants and GE components in the IFS and across the anticipated range of manufacturing conditions, it should not be essential for the PPQ campaign to include all variable features in the IFS or all potential manufacturing conditions.

During continued process verification, the applicant should track and trend process performance and product data across all lots and for each product variant to monitor how variable features impact process performance and product quality. When adding new product variants to a BLA, if the initial process validation was properly designed to cover future product variants and GE components within the IFS, additional process validation will generally not be necessary.

¹⁷ See 21 CFR 211.100(a); 211.110(a); FDA Guidance for Industry: *Process validation: General Principles and Practices*, January 2011, <https://www.fda.gov/media/71021/download>.

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V. ACTIVITY, POTENCY, AND SAFETY OF PRODUCT VARIANTS

A. Activity and Potency Assurance

As for all gene therapy products, FDA recommends that the BLA for an individualized GE product include a potency assurance strategy.¹⁸ Lot release testing must include one or more potency assays as part of the DP release specification.¹⁹ Demonstration of potency for each lot should include confirmation that the GE components achieved the desired editing outcome at or above an acceptance criterion based on data from clinical studies. The assay(s) should be capable of quantitatively assessing the specific contribution of the variable features of the GE components to product potency.

- For *in vivo* individualized GE products, potency assays may warrant developing cell lines that include sequences that match the gene variants targeted by the product. With such cell lines, for example, potency can be measured by transducing the cell with the product, sequencing the targeted site, and measuring successful editing of the gene variant to the intended sequence. Consideration should be given to how the cell lines can be modified to include additional gene variants as new product variants are added to the IFS.
- For *ex vivo* individualized GE products, the pathogenic gene variant is present in the cellular starting material, and the editing outcome should be measured directly in the cellular DP. In addition, a potency assay should assess the intended downstream biological modification (e.g., restoration of enzymatic activity). Applicants should also establish assays to measure activity of the GE components used during manufacturing and appropriate acceptance criteria.

As discussed in Section VI.A, FDA may approve the addition of product variants to the BLA based on *in vitro* safety and activity studies of GE components that have been manufactured by representative processes. The activity studies can potentially use the same potency and/or activity assays discussed in this section. Applicants should establish appropriate acceptance criteria for these assays during clinical development, based on potency data from product lots demonstrated to be clinically effective. For GE components and *in vivo* products, expressing activity or potency as a relative value against a thoroughly characterized reference material can facilitate the establishment of meaningful acceptance criteria. These acceptance criteria create a well-defined threshold that links *in vitro* potency to clinical evidence of effectiveness. This link enables applicants to add new product variants within the established IFS to the BLA based on *in vitro* data and previously submitted clinical data, without conducting clinical studies for each new product variant.

¹⁸ See Draft Guidance for Industry: *Potency Assurance for Cellular and Gene Therapy Products*, December 2023, <https://www.fda.gov/media/175132/download>. When finalized, this guidance will represent FDA's current thinking on this topic.

¹⁹ See 21 CFR 610.10, 600.3(s), 610.1.

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B. Safety Evaluation

Individualized GE products submitted in a BLA should have defined pharmacokinetic, pharmacodynamic, immunogenicity, biodistribution (where applicable), and toxicological profiles supported by nonclinical and clinical studies. Individualized GE product variants included within an established IFS are expected to have the same profiles. Section VI provides criteria for determining when clinical data are expected to be provided in a BLA to support a product variant, for a product that includes multiple product variants.

Safety in the context of off-target or unintended on-target edit outcomes for each product variant should be assessed by the applicant using appropriate *in vitro* methods. The unique gRNA spacer sequence for each product variant creates a distinct off-target editing profile; therefore, applicants should assess the off-target editing risk for each gRNA/editor combination. Applicants should assess unintended editing activities for each product variant using pre-defined next-generation sequencing (NGS)-based methods.²⁰ These methods may be leveraged across product variants.²¹ The applicant should conduct the safety assessment in appropriate target human cells and other human cell types selected based on data obtained from prior nonclinical biodistribution studies, as applicable.²² A protocol detailing the specific methods (e.g., NGS-based nomination, confirmatory testing, etc.) for *in vitro* assessment of the safety of product variants should be submitted with the BLA, which will help streamline the process of adding future product variants without additional clinical data (also see Section VI).

The results from off-target assessment studies should include reports of unintended editing outcomes at the on-target edit site, off-target editing activity(ies), and genomic rearrangement event(s). For all identified and confirmed off-target edit sites, the BLA or BLA supplement should include the corresponding empirical/in silico/sequence homology data (as applicable) and risk assessments discussing clinical significance of all confirmed off-target edit sites.

VI. ADDING NEW PRODUCT VARIANTS TO AN APPROVED BLA

After BLA approval, applicants may submit BLA supplements to add new product variants that target different pathogenic gene variants in the same gene. In most cases, new product variants that fall within the established IFS may be added based on *in vitro* data without the need for

²⁰ See Draft Guidance for Industry: *Safety Assessment of Genome Editing in Human Gene Therapy Products Using Next-Generation Sequencing*, April 2026, <https://www.fda.gov/media/191966/download>. When finalized, this guidance will represent FDA's current thinking on this topic.

²¹ See Draft Guidance for Industry *Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing*, June 2026, <https://www.fda.gov/media/192810/download>. When finalized, this guidance will represent FDA's current thinking on this topic.

²² See Draft Guidance for Industry *Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause*, February 2026, <https://www.fda.gov/media/191247/download>. When finalized, this guidance will represent FDA's current thinking on this topic.

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additional clinical data, as described in Section III. This section describes the regulatory mechanisms for doing so after BLA approval, including the data that applicants should provide to add a new product variant within the established IFS (Section VI.A) and to expand the established IFS (Section VI.B).

A. Adding a New Product Variant Within an Established IFS

Adding a new product variant to an existing BLA is a change to the product's manufacturing, and the applicant must submit a BLA supplement demonstrating that the change does not adversely affect the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.²³ When submitting a BLA supplement to add one or more new product variants within the established IFS, the submission should contain *in vitro* activity data demonstrating the ability of each new product variant to achieve the intended edit at or above a threshold established in clinical studies. Additionally, the supplement should include *in vitro* safety data for each new product variant, including comprehensive on-target and off-target editing analyses, demonstrating that off-target editing profiles remain within acceptable limits and risk profile. The supplement must update the manufacturing information to include the new product variants and must update the labeling to list the new gene variants targeted.²⁴

The *in vitro* safety and activity studies submitted in a BLA supplement may use GE components manufactured by representative processes (including scaled-down processes) prior to the manufacture of lots produced in accordance with Current Good Manufacturing Practice (CGMP). However, the purity, chemistry, and structure of the GE components used in the *in vitro* studies (e.g., modified RNA bases and backbone linkages) should be equivalent to those of the intended commercial GE components. If the BLA supplement is approved, the product variant must be manufactured in compliance with CGMP requirements and meet all established release specifications prior to commercial distribution.²⁵

If the relationship between the product's *in vitro* data and clinical safety and effectiveness is well-understood and predictable, FDA generally does not expect clinical data to be included in BLA supplements that add new product variants. Applicants should justify how the variants evaluated in the initial clinical studies represent the full range of variability and anticipated risk factors across the entire established IFS. If the relationship between the product's *in vitro* data and clinical safety and effectiveness is not well-understood or predictable for any specific new product variant, the BLA supplement should include adequate clinical data from subjects who received that product variant. It is important that applicants discuss their specific plan with FDA prior to data collection and BLA supplement submission to get FDA feedback on the evidence package necessary to support addition of new product variants to the BLA.

²³ 21 CFR 601.12(a)(2).

²⁴ 21 CFR 601.12.

²⁵ 21 CFR 210, 211, and 610; 21 U.S.C. 351(a)(2)(B).

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To facilitate adding product variants within the established IFS after approval, FDA recommends that applicants submit and receive approval for a postapproval change management protocol (PACMP) under 21 CFR 601.12(e).²⁶ A PACMP is a protocol submitted to FDA that describes, in advance, the specific changes an applicant anticipates making postapproval, the data and studies that will be conducted to assess each change, and a proposed reporting category under which each change will be submitted.²⁷ A well-designed PACMP with clear procedures and criteria will provide an agreed-upon, predictable way to add new product variants to the BLA. For individualized GE products, a PACMP for adding new product variants within the established IFS should describe the *in vitro* activity and safety data that will be generated for each new product variant and how those data will be evaluated.

B. Expanding an Established IFS

An applicant may seek to expand the boundaries of an established IFS in an approved BLA to allow inclusion of product variants that do not fit within the established IFS. Expanding the IFS has a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product, and therefore this type of change must be submitted to the BLA as a prior approval supplement.²⁸

The amount and type of evidence needed to support an expansion of the IFS should be informed by a thorough risk assessment. In certain circumstances, FDA expects that the safety and effectiveness of a product with an expanded IFS can be assured by *in vitro* studies (in addition to clinical data already submitted for other variants), and in these cases additional clinical studies will not be expected. Notably, the risk assessment and the scope of any clinical data provided to support an IFS expansion should be informed by an understanding of how the product's variable features relate to safety and effectiveness. For example, FDA would not expect clinical data to be provided for the addition of a new editor with conservative changes in its PAM-recognition sites if a risk assessment and *in vitro* data demonstrate that the effects of these changes on product variant safety and activity are well understood and predictable.

If a proposed expansion in the IFS involves a change that would fundamentally alter the design of the product or introduce significant new or unknown risks to the identity, strength, quality, purity, or potency of the product as they may relate to the safety or

²⁶ See also Guidance for Industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*, May 2021, <https://www.fda.gov/media/148476/download>.

²⁷ See Guidance for Industry *Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA*, October 2022, <https://www.fda.gov/media/162263/download> (The use of “Comparability protocol” in this guidance is synonymous with “postapproval change management protocol” in the International Council for Harmonisation (ICH) guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management and its Annexes* (May 2021) (ICH Q12)).

²⁸ 21 CFR 601.12(b).

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effectiveness of the product – for example, adding a reverse transcriptase-based editor to a product that is approved to use an adenine base editor – it would not be appropriate to submit the change as a supplement to the current BLA. Such changes represent a new product and should be submitted in a new BLA. See Section III for additional guidance on distinguishing IFS expansions from changes that require a new BLA.

VII. PRODUCT LABELING AND NAMING

A. Labeling Considerations

Labeling for individualized GE products will be required to comply with relevant statutory and regulatory requirements.²⁹ The labeling of such products must include the standard sections of the prescribing information and the evidence supporting product approval.³⁰ The Indications and Usage³¹ section of the prescribing information (section 1) for an individualized GE product should reflect the scientific evidence that supports approval and should concisely communicate the use(s) for which the GE product has been shown to be safe and effective. All indications listed in this section must be supported by substantial evidence of effectiveness.³²

The indicated population in the Indications and Usage section should reflect the disease and associated gene variants or class of gene variants (e.g., pathogenic C>T or G>A base substitution) for which safety and effectiveness were demonstrated in clinical studies. If the indicated population is intended to be limited to specific gene variants within a class of gene variants, the Indications and Usage section should clearly convey that the scope of approval is limited to those specific gene variants. Each specific gene variant within the scope of the approval could be explicitly referenced in the Indications and Usage section itself, or by a clear cross-reference to another section of the prescribing information where gene variants are listed (e.g., Mechanism of Action (section 12.1)). Regardless of whether the specific gene variants are listed in the Indications and Usage section explicitly or by a clear cross-reference to another section, the listing should specify which gene variants were evaluated in clinical studies.

After initial BLA approval, additional product variants that meet the established *in vitro* safety and activity criteria for editing the corresponding pathogenic gene variants may be considered for addition to the BLA and inclusion in the labeling. When additional gene variants are determined to be appropriate for inclusion in the labeling, they could be added to the Indications and Usage section of the prescribing information or to the list of

²⁹ See, e.g., sections 502(a) and 502(f) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 CFR 201.56, 201.57, 201.100.

³⁰ 21 CFR 201.57.

³¹ See Draft Guidance for Industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*, July 2018, <https://www.fda.gov/media/114443/download>. When finalized, this guidance will represent FDA's current thinking on this topic.

³² 21 CFR 201.57(c)(2)(v).

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variants in section 12.1 (which would be cross-referenced in the Indications and Usage section), along with the type(s) of data (clinical or *in vitro*) supporting such addition.

In cases where different pathogenic gene variants in the same gene cause clinically distinct diseases or conditions, adding a product variant that targets a gene variant associated with a different disease or condition than the approved indication – even if the gene variant is in the same gene and the editing outcome is the same – would constitute a new indication that should be supported by clinical evidence and should not be added to the BLA solely on the basis of *in vitro* studies and clinical data previously submitted in support of a different indication.

B. Product Naming and Identification

An approved BLA for an individualized GE product contains a single product, even though it uses approved product variants to address patient-specific gene variants. All approved product variants of a single individualized GE product are considered to have the same active ingredient. Therefore, the product’s proprietary name and nonproprietary name³³ should not distinguish among product variants. Because product variants of an individualized GE product should not differ in any attribute that would require a new product code under 21 CFR 207.35, a separate National Drug Code (NDC) is not required for each product variant; therefore, the NDCs in the product’s labeling should apply to all product variants.

Container and package labels must include a lot number or other lot identification.³⁴ Container and package labels should also include a separate identifier sufficient to allow confirmation that the correct product variant has been dispensed. This product variant identifier should consist of the specific gene variant or corresponding protein variant targeted by that lot of the product. For example, labels should include a field such as “Targeted gene variant: [xxxxx].” FDA does not recommend using the names of the GE components in the labeling, as an identifier describing the targeted gene variant provides more meaningful information for physicians and patients.

If risk assessment warrants patient-specific labeling to mitigate the risk that a patient might receive the wrong product variant, the package should include one or more patient-specific identifiers linking the lot to the intended recipient. For autologous *ex vivo*

³³ The nonproprietary name for non-autologous products should have a suffix that is devoid of meaning and composed of four lowercase letters. See Guidance for Industry *Nonproprietary Naming of Biological Products*, January 2017, <https://www.fda.gov/media/93218/download>. The nonproprietary name of an autologous product does not need a suffix because robust identification practices exist to ensure safe dispensing and optimal pharmacovigilance. See *SOPP 8426: Assignment of Biological and Drug Product Proper Names and Biological Suffixes*, September 28, 2026, <https://www.fda.gov/media/96219/download?attachment>.

³⁴ See 21 CFR 610.60(a)(3) and 610.61(c).

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products, FDA recommends that at least two unique patient-specific identifiers appear on both the container and package labels.³⁵

VIII. DEFINITIONS

Genome editing component: Any material that is essential for the intended genomic modification, including those that may not appear in the final drug product. Genome editing 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.

Individualized feature space (IFS): The allowable limits of variation for one or more variable features of a product's genome editing components. An IFS includes only features or combinations of features known or predicted to have adequate safety and activity. Adding a new product variant within a pre-defined IFS should not be considered to result in a new product.

Individualized genome editing product: A genome editing product where the genome editing components are designed to have variable physical features that are matched to specific patients or patient subgroups to address patient-specific gene variants.

Monogenic disease: A disease caused by a pathogenic gene variant in a single gene, also known as a single-gene disorder or Mendelian disorder.

Pathogenic gene variant: A permanent change in the wild-type DNA sequence of a gene in the human genome that causes a monogenic disease.

Product variant: A specific instance of an individualized GE product where one or more physical features have been deliberately selected or modified to target a gene variant. A product variant maintains the core design of the product and shares the same IND or BLA with other product variants.

Variable feature: A physical characteristic of a genome editing component that differs from lot to lot, within defined limits, to address specific gene variants.

Guidance History	Date	Description
Level 1 Draft Guidance	October 2026	See Notice of Availability for more information.*

*The Notice of Availability is accessible via the [Search for FDA Guidance Documents webpage](#).

³⁵ For additional recommendations on using unique identifiers for autologous *ex vivo* products, refer to Guidance for Industry *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products*, January 2024, <https://www.fda.gov/media/156896/download>.