Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause

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Draft Guidance for Industry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 (CBER)
Center for Drug Evaluation and Research (CDER)
February 2026

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Contains Nonbinding Recommendations

Draft – Not for Implementation

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Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to describe considerations for generating substantial evidence of effectiveness and evidence of safety for individualized therapies[2] based on a plausible mechanism framework. The plausible mechanism framework outlines a set of recommendations to help developers of individualized therapies generate sufficient clinical safety and efficacy data to demonstrate that a drug or biological product is safe and effective for the intended use, and that the product can be manufactured to regulatory quality standards. These data are used to support approval or licensure of an individualized therapy for a specific indication. This includes a careful evaluation of the results of nonclinical and clinical data and chemistry, manufacturing, and controls (CMC) data necessary to support product quality. Application of the plausible mechanism framework involves:

- Identifying a specific genetic, cellular, or molecular abnormality with a clear connection between specific alteration and disease indication
- Developing a therapy that targets the underlying or proximate pathogenic biological alterations
- Relying on a well-characterized natural history of the disease in an untreated population
- Confirming that the target was successfully drugged or edited or both
- Demonstrating improvement in clinical outcomes or course

For the purposes of this guidance, individualized therapies are considered therapies that target a specific pathophysiologic abnormality serving as the root cause of a disease, for example, specific pathogenic genetic variant(s) causing a severely debilitating or life-threatening disease

[1] This guidance has been prepared by the Office of Therapeutic Products in the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *therapy* or *therapies* refer to human drugs and therapeutic biological products unless otherwise indicated.

or condition in a small number of patients where a randomized controlled trial typically is not feasible.

While this guidance specifically discusses genome editing (GE) and RNA-based therapies (e.g., antisense oligonucleotides (ASOs)), the general concepts may apply to other types of individualized therapies. Specifically, this guidance applies when clinical evidence from a limited number of patients will be available to support the individualized product's safety or efficacy in the intended patient population.

The guidance discusses the circumstances in which data generated from individualized therapies may be adequate to support approval under existing regulatory approval pathways. This guidance expands upon FDA's current thinking regarding drug[3] development and clinical trial design issues for individualized therapies for the treatment of rare genetic disorders.[4] The recommendations in this guidance are consistent with the publication, "FDA's New Plausible Mechanism Pathway," and are informed by the workshop, "Individualized Therapies on the RISE."[5]

This guidance does not provide recommendations on the following:[6,7]

- Discipline-specific content and format of an NDA/BLA submission
- Specific development programs, including patient populations, endpoints, or specific approval pathways (accelerated vs. traditional)

These topics should be discussed with the relevant review division for a specific development program. Case examples provided are for illustrative purposes only and do not endorse any specific disease population or endpoints.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of

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[3] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[4] See the guidances for industry *Rare Diseases, Considerations for the Development of Drugs and Biological Products* (December 2023) and *Human Gene Therapy Products Incorporating Human Genome Editing* (January 2024). See also the draft guidance for sponsor-investigators *IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations* (December 2021).

[5] Duke-Margolis Institute for Health Policy FDA Convening Individualized Therapies of the RISE; November 20, 2025.

[6] See the draft guidance for sponsor-investigators *Investigational New Drug Application Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations* (December 2021).

[7] See the draft guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023).

the word *should* in Agency guidances means that something is suggested or recommended but not required.

II. BACKGROUND

Recent scientific and technological advances have increased the ability to characterize the molecular changes that underlie an individual's genetic disease (e.g., missense mutations, gene deletions, rearrangements) and allow for the development of therapies that are targeted to those changes. These advances provide an opportunity to treat patients who have rare, severely debilitating, or life-threatening diseases (SDLT) with therapies that are targeted to their unique gene variant. Often, these diseases are rapidly progressing, resulting in early death and/or devastating or irreversible morbidity within a short time frame without treatment and have no treatment options. In many cases, it may not be feasible for development programs to conduct randomized, controlled trials in a larger number of patients with the same disease because of the specificity of the mechanism of action of the individualized therapy and the rarity of the treatment-amenable patient population. In the past FDA provided guidance that describes general approaches to evaluating the benefits and risks of targeted therapeutics within a clinically defined disease where some molecular alterations may occur at low frequencies.[8] However, that guidance did not cover the individualized therapies covered in this document where clinical evidence is more limited. Additionally, while other FDA guidance documents discuss general approaches to the demonstration of substantial evidence of effectiveness[9] or the application of particular trial designs, including single arm trials utilizing participants as their own controls,[10] adaptive trial designs,[11] and externally controlled trials,[12] it may be challenging to apply these approaches in the context of the individualized therapies described in this guidance where the first-in-human study may be designed as a pivotal trial to support approval.

The Agency recognizes the importance of the approval of safe and effective individualized therapies that may allow for greater access and encourage further scientific advances to continue development of treatments for a broader scope of rare diseases. Therefore, the tolerance of risk

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[8] See the guidance for industry *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease* (October 2018).

[9] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998). See also the draft guidances for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) and *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023).

[10] See the draft guidance for industry *Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations* (September 2025), at 3. When finalized, this guidance will represent FDA's current thinking on this topic.

[11] See the guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* (December 2019).

[12] See the draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023). When finalized, this guidance will represent FDA's current thinking on this topic.

is contingent on the benefit-risk assessment which will be considered during the review of a marketing application. Although typical therapeutic development programs may not be feasible for individualized therapies in a very small number of patients, it may still be possible to generate data to establish safety and provide substantial evidence of effectiveness to support the marketing approval of the product under existing regulatory approval pathways. Here, the Agency will consider the safety of these products in the context of the underlying SDLT with limited or no treatment options, therapeutic efficacy, and the ability to mitigate the onset and resolution of local and systemic toxicities and immunogenicity. The Agency anticipates that substantial evidence of effectiveness for individualized therapies could be established based on a single adequate and well-controlled clinical investigation with confirmatory evidence.

The individualized therapies discussed in this guidance are limited to diseases that have a well-characterized, identifiable molecular or cellular abnormality, and the therapeutic product targets the underlying abnormality, its proximal pathogenic pathway, or a well-characterized downstream or compensatory mechanism with a clear mechanistic rationale. Nonclinical data that support sufficient editing or target engagement are needed to justify initiation of treatment in humans and may also provide confirmatory evidence.[13] In patients for whom the natural history of the disease in the untreated state can be reasonably characterized, it may be possible for an externally controlled clinical investigation that assesses a patient's change following treatment compared to baseline to serve as the adequate and well-controlled clinical investigation necessary to support approval/licensure. A substantial improvement in symptoms or change in disease trajectory that is inconsistent with the natural history of the disease may provide substantial evidence of effectiveness. The data submitted by the sponsor must adequately demonstrate that the improvement in outcome cannot reasonably be attributed to alternative treatments or natural variability in the disease phenotype.

For sponsors who intend to submit a marketing application for an individualized therapy, planning for evidence generation to support the efficacy and safety of the product should ideally begin as soon as the patient and genetic target are identified. Given the inherent limitations in the size of clinical development programs, early planning will allow more robust collection of data from various sources, which have the potential to be leveraged as evidence to support a future marketing application. Planning should also include establishing the appropriate chemistry, manufacturing, and controls (CMC) needed to support the generation of safety and efficacy data and subsequently, product approval/licensure.

Many diseases, particularly rare diseases, can be caused by a variety of different mutations within a single gene (e.g., beta-thalassemia, phenylketonuria). Genetically targeted therapies amenable to treatment of rare genetic disorders, including genetic variants that are unique to individual patients, include GE technologies and RNA-targeted therapies. RNA-targeted therapies, such as ASOs and small interfering RNAs, target specific RNA sequences to modulate gene expression by altering mRNA levels to reduce disease severity. In some cases, the activity of RNA-targeted therapies can be highly specific to the patient's genetic variant, but these

[13] See 21 CFR 312.23(a)(8).

products can also act through target modulation that is not specific to a single pathogenic variant (and thus be active against multiple genetic variants). 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 (e.g., CRISPR-Cas, ZFNs, TALENs) or nickase-dependent (e.g., base editing, prime editing) GE technologies. GE technologies are designed to be highly specific to unique DNA sequences. Thus, current GE technologies are able to correct many single gene mutations. Moreover, many GE technologies can be considered modular in that each product is composed of multiple components (e.g., editors, guide RNA [gRNA], donor templates, etc.) that can be modified independently. These types of GE products may be designed to treat diseases caused by many different mutations within a single gene by modifying a single GE component. For example, when utilizing a CRISPR system in a product, if different gRNA are needed to target different mutations in a single gene, the product "variants" incorporating these gRNA may be included in a single IND/BLA, if the method of correction is the same between the gRNA (e.g., return to the normal/native gene sequence). Under this paradigm, nonclinical and clinical data could be collected using a defined set of mutations to support product licensure. A highly supported "plausible" mechanism of action may then be used to support the addition of other such GE product variants, intended to treat patients with mutations that were not included in the clinical trial used to support the original approval.

III. DISCUSSION

A. Regulatory Pathway

As noted above, approval of an individualized therapy as described in this document would, as with other drugs, require substantial evidence of the drug's effectiveness for its intended use and sufficient information to conclude that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.[14] In applying the effectiveness standard to individualized therapies, FDA takes into consideration the clinical context for the disease, the level of unmet medical need, and the challenges involved in enrolling participants in a clinical investigation for an individualized therapy.[15]

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[14] See section 505(d) of the FD&C Act (21 U.S.C. 355(d)). Under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), licenses for biologics have been issued only upon a showing that the products are "safe, pure, and potent[.]" Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). FDA has also generally considered substantial evidence of effectiveness to be necessary to support licensure of a biological product under section 351 of the PHS Act. FDA has proposed recommendations regarding the demonstration of substantial evidence of effectiveness in the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When finalized, this guidance will represent FDA's current thinking on this topic.

[15] See the guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023).

- Substantial evidence of effectiveness may be provided in accordance with the criteria discussed in section III.B. of this guidance using an approach of a single adequate and well-controlled clinical investigation with confirmatory evidence.

- FDA recognizes that an adequate and well-controlled clinical investigation in this context will include a small sample size, therefore, investigation results should be robust to exclude chance findings that may incorrectly suggest effectiveness.

- Confirmatory evidence would likely come from clinical or nonclinical data sources and may include but are not limited to:

    - Mechanistic or pharmacodynamic data
    - Confirmation of target engagement based on nonclinical or clinical data
    - Exposure-response on biomarkers and clinical outcomes

- Approval of an individualized therapy as described in this document may occur through the traditional approval pathway or the accelerated approval pathway depending on the endpoints used in the clinical investigation. For drug development programs intending to seek accelerated approval, FDA generally intends to require that the confirmatory study be underway prior to the accelerated approval action.[16]

- At the time of submission of a marketing application, safety data will be limited by the small number of patients treated; however, FDA may require that data on safety continue to be collected in the post-marketing setting.[17] This may also include collection of efficacy outcomes if there is evidence of a potential for loss of efficacy over time. Refer to section III.B in this guidance for more details.

- FDA also intends to closely monitor reports of adverse events from the trial and any signals of unexpected or delayed adverse events in the post-market setting. If a safety signal emerges, FDA will investigate the signal to determine if any action is warranted.

- Benefit-risk assessment will be considered during the review of a marketing application.

[16] See section 506(c)(2)(D) of the FD&C Act (21 U.S.C. 356(c)(2)(D)). See also the draft guidances for industry *Expedited Program for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024) and *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway* (January 2025). When finalized, these guidances will represent FDA's current thinking on these topics.

[17] See section 506(c)(2)(C) of the FD&C Act (21 U.S.C. 356(c)(2)(C)).

B. Nonclinical

This section outlines the goals of nonclinical programs to support individualized GE and ASO products and discusses regulatory flexibilities and opportunities for data leveraging.

- The overall objectives of the nonclinical program are to demonstrate proof of concept (POC) and safety to support initiation of the first-in-human (FIH) study. The nonclinical studies should establish the feasibility of the proposed clinical route of administration, support the scientific rationale for product administration, and identify potential risks.

- Per 21 CFR 312.23(a)(8), the sponsor must provide adequate information about pharmacological and toxicological studies on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.

- Nonclinical data may be supplied to demonstrate the prospect of direct benefit required for enrollment of pediatric participants in the FIH investigation in accordance with 21 CFR 50.52.

- FDA may exercise regulatory flexibility regarding the design of the nonclinical program, including the study duration, types of studies needed, and model selection for individualized therapies using GE or ASO products with a specific and well-characterized mechanism of action for rare diseases.

  The use of New Approach Methodologies (NAMs) (e.g., cell-based, organoid, in silico, in chemico methods, etc.) is encouraged whenever appropriate. Sponsors should seek early feedback on their nonclinical development plans to discuss the incorporation of NAMs.

- For considerations regarding the design of the nonclinical POC and safety studies, please refer to the following guidance documents:

  - GE products:
    - Guidance for Industry: Human Gene Therapy Products Incorporating Human Genome Editing (January 2024)
    - Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)

- ASO products:
  - Draft Guidance for Sponsor-Investigators: Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases (April 2021)[18]

FDA recommends that sponsors discuss their proposed nonclinical development programs with the Agency early in product development.[19]

GE products

POC study recommendations for the FIH trial

- POC studies should be conducted in an appropriate model. In vitro systems such as patient cells, engineered human cells, or NAMs should be representative of the target cell/tissue and harbor the genetic sequence amenable for GE. POC studies may be conducted with the intended clinical product or a species-specific analogous GE product. If an analogous GE product is used, sponsors should provide scientific justification to establish the biological relevance of the analogous product compared to the intended clinical product. Studies should provide sufficient evidence to support the intended level of editing at the proposed clinical dose levels, route of administration, and dosing regimen, in the proposed clinical trial.

- Evaluation of GE outcomes resulting in intended edits (e.g., percent on-target editing efficiency) should be assessed with next-generation sequencing (NGS)-based methods.

- To expedite nonclinical development, a single hybrid definitive POC/safety/distribution study may be conducted to evaluate product safety and activity. The definitive hybrid study design should be based on pilot data, which may be generated from in vitro and in vivo studies. Pilot data should guide the selection of an appropriate model, inform the dose level range for the definitive study, and support the mechanism of action of the product.

Safety assessment recommendations for the FIH trial

- The safety assessments for in vivo GE products should comprehensively characterize the risks (e.g., onset and resolution of local and systemic toxicities and immunogenicity) associated with the delivery vector, delivery components (as applicable), and/or GE components. The immunogenicity assessment should also

[18] When final, this guidance will represent the FDA's current thinking on this topic.

[19] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

evaluate risks associated with repeat dosing and/or intra-patient dose escalation, as applicable.

- Biodistribution (BD) and elimination of both the delivery components (e.g., novel lipid nanoparticles, adeno-associated vector capsids, etc.) and the GE components (e.g., mRNA, transgene, editor protein) should be evaluated for in vivo GE products. Cell distribution, survival/engraftment (as applicable), proliferation, and phenotype should be evaluated for ex vivo GE products.

- Organ-specific assessments may be requested on a case-by-case basis, depending on the BD of the product. For example, safety pharmacology assessments may be necessary and may be incorporated into the definitive safety study, if the product distributes to the heart, lungs, or central nervous system.

- Nonclinical studies to evaluate unintended editing outcomes at the target site, off-target editing risk, and impact of GE on chromosomal integrity should be conducted in appropriate target human cells and other human cell types selected based on data obtained from BD studies. These studies should use NGS-based methods to facilitate detection and reporting of low frequency off-target editing events and changes to genome integrity. FDA intends to provide additional recommendations on nonclinical studies using NGS-based methods that may be needed to support the initiation of clinical trials of investigational human GE products in the near future.

Opportunities for leveraging data

- There may be opportunities to leverage POC and safety data and bioinformatics knowledge between clinical programs using multiple gRNAs and/or different versions of a genome editor. Sponsors should seek early feedback on their nonclinical development plans to discuss data leveraging opportunities specific to their program.

- If leveraging data and knowledge is anticipated, editing activity at the target site and off-target editing risk should be evaluated for each product variant. Sponsors are encouraged to develop appropriate cell systems and/or assays to facilitate reliable evaluation of editing activity for a range of product variations that may include different gRNA and editor combinations. For example, an engineered cell line expressing the target genomic sequence(s) may be used to evaluate each product variant. In addition, sufficient data should be provided to support the dose level for all product variants prior to human administration. Sponsors are encouraged to develop an appropriate dose selection strategy that will facilitate identification of the dose level for a range of product variants during early development.

Studies to support approval, and to add new targets to a BLA

- Depending on the BD profile, patient population, and the risks associated with the product, Developmental and Reproductive Toxicology studies may be warranted to support BLA approval.

- To add a product variant that targets a mutation that has not been evaluated in the clinical trial to the BLA, in vitro activity data should be provided for the specific product variant to support editing activity at the target site, and an off-target editing activity assessment should be performed to support safety.[20]

ASOs

POC study recommendations for the FIH trial

POC studies should provide rigorous scientific evidence as follows:

- Primary pharmacology studies should investigate the mode of action and/or effects of an ASO in relation to its desired therapeutic target.

- Mechanistic evidence supporting that a specific genetic mutation is the cause of the disease pathophysiology.

- Scientifically valid information describing the known gene target biology inclusive of the consequence of the loss of expression as well as over-expression of the genetic target.

- Studies, including in vitro assays or NAMs, that provide evidence of a biological response due to the ASO and correction of the disease-causing mutation in the target tissue(s).

- When POC data are available from any relevant model, these should be submitted (can be studies published in the scientific literature or publicly shared information).

Safety assessment recommendations for the FIH trial

An abbreviated nonclinical program can be used to support patient safety, due to the unique benefit-risk profile of individualized therapies; however, the ASO should be from a well-characterized chemical class for which there is substantial nonclinical information

[20] Additional nonclinical studies may be needed depending on the characteristics of each product variant. We encourage early interaction with OTP for feedback on data submission requirements.

to inform safety. The following are nonclinical recommendations to assess the safety of the ASO, with additional proposed recommendations included in the Draft Guidance for Sponsor-Investigators: Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases (April 2021).[21]

- High level study design elements should incorporate the following: core safety pharmacology endpoints are included depending on the route of administration, a standard battery of toxicologic endpoints, and exploration of a full dose range to the MTD or MFD should be explored to support the safety of human dose escalation. The nonclinical study should incorporate the same route of administration, formulation, and dosing regimen as used in humans, when feasible. If scientifically relevant ASO and genetic disease related toxicity data is publicly available (or is available by right of reference), we encourage its submission.

- FDA encourages Sponsors to consider methodologies such as in vitro cell-based studies and NAMs.

- Hybridization-dependent off-target assessment: Sponsors should use suitable methodologies available at the time of their product development including appropriate in silico and/or in vitro approaches to assess possible off-target binding.

- Well-characterized ASO chemistries have been observed to have toxicologic risks in non-human models that may translate to humans, and these endpoints should be routinely monitored in humans (e.g., kidney or liver toxicities, potential for acute phase reactions).

- For those ASO products that are not from a well-characterized chemical class, a more traditional nonclinical program may be needed, and should be discussed with the review division.

Studies to support approval

- Following initial evaluation of the ASO safety profile, additional nonclinical studies may be warranted if unexpected or significant toxicity is observed, there is new information available that changes the benefit-risk profile, or if a new route of administration has the potential to alter the toxicity profile (e.g., not the expected toxicity due to the known risks of well-characterized ASOs). FDA encourages the use of appropriate NAMs in these cases.

[21] When final, this guidance will represent the FDA's current thinking on this topic.

- Depending on the patient population and the benefit-risk profile of the ASO, Embryo-Fetal Development (EFD) studies or a weight-of evidence (WoE) assessment showing potential for reproductive toxicity, may be warranted to support approval.

C. Clinical

Given the very small number of patients expected to be treated, early planning is critical to identify the potential sources of efficacy and safety data for the product to support a future marketing application. FDA anticipates that the first-in-human clinical investigation that will open an IND will also be the primary source of evidence to support approval; therefore, protocols should be designed to be adequate and well-controlled in accordance with at 21 CFR 314.126.[22] A justification should be provided for the design of the clinical study, including a discussion of why it is not feasible to conduct a randomized controlled trial.

Additionally, it is important to identify potential clinical outcomes and biomarkers that are relevant to the disease and systematically collect this data in patients eligible for treatment prior to initiation of the individualized therapy. Sponsors should initiate an observational protocol to collect such data as soon as the potential study participants are identified while other early product development activities are being conducted (e.g., manufacturing, nonclinical studies). This will allow for piloting clinical outcome assessments, identifying disease-relevant biomarkers, establishing the lead-in baseline, and characterizing disease trajectory. This may also be the optimal time to identify and obtain sources of natural history data.[23]

Ethical and Human Subject Protection Considerations

- Under FDA regulations, a protocol under which the investigational product is administered to a human subject must be reviewed and approved by an institutional review board (IRB) before it is allowed to proceed (21 CFR part 56).

- If children are to be included in the protocol, the requirements in 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations) also must be met.

[22] Although biological products licensed under section 351 of the PHS Act are not subject to 21 CFR part 314, when determining whether a clinical investigation for a biological product is adequate and well-controlled, FDA generally considers the characteristics outlined in 21 CFR 314.126.

[23] Additional information regarding the use and design of natural history studies for rare diseases can be found in the *Guidance for Industry: Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023) and *Draft Guidance for Industry: Rare Diseases: Natural History Studies for Drug Development* (March 2019). When final, this guidance will represent the FDA's current thinking on this topic.

- In accordance with 21 CFR 50.20, the sponsor must obtain legally effective informed consent that includes all the required basic elements under 21 CFR 50.25(a) from the trial participant, or the participant's legally authorized representative, before administration of the investigational product.

- For additional discussion of ethical considerations for individualized therapies, see to the Draft Guidance for Sponsor-Investigators: IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations (December 2021).[24]

Design of the clinical investigation

- Protocols should be designed with standardized, prespecified assessments of clinical efficacy and safety outcomes and relevant biomarkers.

- Analysis plans for the data compared to a control should be pre-specified.

- It is recommended that data be collected in an observational period prior to the initiation of the treatment to establish a lead-in baseline.

- In general, the disease under study will have a well-characterized natural history in the untreated population. This natural history data may serve as an external control if it is adequate to allow for the treatment effect to be reasonably distinguished from natural variability in the phenotype of the disease.[25]

- FDA recognizes that some diseases may have a more variable or episodic course and will consider investigation designs (e.g., longer duration of follow-up) or measures of benefit (e.g., surrogate endpoints) that may support demonstration of a treatment effect.

- As described in the Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials (May 2001), if the effect of a treatment is dramatic or self-evident, occurs rapidly following treatment, and is unlikely to have occurred spontaneously, it may be acceptable in some situations to compare a change from baseline to an estimate of what would have happened to the patient in the absence of the treatment with the intervention. This estimate may be based on available natural history data, general knowledge of the disease, or the baseline lead-in period.

[24] When final, this guidance will represent the FDA's current thinking on this topic.

[25] For further recommendation regarding the conduct of externally controlled trials, see the draft guidance for industry: *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023). When final, this guidance will represent FDA's current thinking on this topic.

- When the effects of the drug on clinical outcomes are not obvious (e.g., because functional losses are more slowly progressive), robust natural history data will likely be necessary to serve as an external control.

- The Agency is open to the use of master protocols (e.g., umbrella or platform trials) for the evaluation of therapies that target different genetic changes for the same disease.[26] Master protocols have the potential to streamline processes and allow for larger scale data collection and sharing to advance science. Plans for the use of a master protocol should be discussed with the appropriate review division prior to initiation of the study.

Establishing genetic mutation/diagnosis[27]

- Sponsors should confirm the patient's diagnosis using appropriate laboratory testing (e.g., sequencing, biochemical or enzymatic tests, imaging) and should validate assays for their intended use and include all results in the NDA/BLA submission.

- Sponsors should provide evidence that the targeted genetic variant(s) play a causal role in the disease before initiating treatment.

- Sponsors should demonstrate that the targeted genetic variant(s) are unique to the patient(s), including prevalence estimates in the disease population and projected incidence in new cases based on molecular genetic characteristics.

Dosing[28]

- Sponsors should select a pharmacologically active starting dose based on nonclinical data, interspecies scaling, and relevant ASO or GE product class or clinical experience.

- For therapies that require multiple doses, sponsors should justify dosing interval, escalation scheme, and any loading or maintenance doses based on pharmacodynamic (PD), pharmacokinetic (PK), tissue distribution, and anticipated toxicities.

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[26] See the draft guidance for industry *Master Protocols for Drug and Biological Product Development* (December 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[27] For additional information, refer to the draft guidance for sponsor-investigators *IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations* (December 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[28] *Ibid.*

- For ASOs, PD biomarkers are likely essential to support optimization of the dose and administration interval for maintenance therapy.

- Some direct PD biomarkers (e.g., RNA or protein products of the targeted sequence) may be difficult to quantify (e.g., membrane-bound proteins in the CNS); however, sponsors should use available methodologies to quantify target engagement.

- For GE therapies, it is expected that consideration be given to whether treatment will consist of a single dose or if repeat administration may be necessary. This should be guided by tissue target(s) and product tropism, patient factors such as age (e.g., scaled doses based on brain weight or expected liver growth), and expected immune responses to the product (e.g., anti-drug antibodies that may preclude further dosing).

- Intra-patient dose escalation is generally recommended for individualized ASO products and may be appropriate in some circumstances for select GE products.

Trial Outcomes

Clinical Outcomes

- As described in the Guidance for Industry: Rare Diseases: Considerations for the Development of Drugs and Biological Products (December 2023), developers should identify clinically meaningful concepts and measure them in a standardized and rigorous manner that would demonstrate clinical benefit (e.g., improvement in symptoms, stabilization or slowing of disease progression, or decrease in frequency or severity of episodic serious disease-related events that is inconsistent with the course of the disease in the untreated state). Determination of concepts to be measured should be done a priori during protocol development with input from disease subject matter experts and patients/families. When possible, leverage existing scales, if they are appropriate for the condition.

- Consider collecting multiple types of outcomes to evaluate for treatment effects.

- Outcomes should be similar to what has been collected in the natural history studies for the disease and the observational baseline lead-in period.

Biomarker Assessments

- Biomarkers may potentially provide evidence to support effectiveness as either surrogate endpoints or as confirmatory evidence. Biomarkers may also support proof of concept, confirm target engagement, inform the need for dose escalation (see *Dosing* section in this guidance), and identify safety issues.

- Biomarker assessments may be used to provide evidence of effectiveness to support traditional approval if they are established to predict clinical benefit (i.e., validated surrogate endpoint) or accelerated approval if they are found to be reasonably likely to predict clinical benefit (i.e., reasonably likely surrogate endpoint).[29]

- Biomarkers that directly reflect disease pathology or that have been previously used to support drug approval[30] are generally the most informative with respect to demonstrating benefit. Determining whether a biomarker predicts clinical benefit (or is reasonably likely to predict clinical benefit) depends on an understanding of the role of the biomarker in the causal pathway of the disease and of the relationship between the drug's effect and the disease process.[31]

- Biomarker assessments used for demonstrating efficacy should ideally be performed using analytically validated methods/assays and preanalytical specimen handling should follow defined procedures.

- Assessment of biomarker(s) that directly measure target engagement or primary pharmacodynamics is likely essential (see *Dosing* section in this guidance). Exploratory biomarker assessments (e.g., metabolomic studies) should also be considered.

- Sponsors should plan for comprehensive biomarker assessments (e.g., molecular, physiological, radiologic) throughout the course of treatment and procure specimens or data using standardized procedures.

Safety Outcomes

- Safety monitoring should be informed by nonclinical toxicology findings, potential off-target gene knockdown effects predicted by bioinformatic tools, and previously identified safety risks associated with the use of similar products in other programs or disease-specific risks.

- Consider use of subject-level stopping rules and allowing for some clinical judgment of clinicians (e.g., in a rapidly fatal disease if left untreated, it may still be reasonable to continue treating a patient who experiences a Grade 3 Drug-induced liver injury (DILI) if they are deriving benefit and the DILI is easily manageable with increased immunosuppression).

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[29] See the draft guidance for industry *Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics* (December 2024). When final, this guidance will represent the FDA's current thinking on this topic.
[30] See the FDA Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure.
[31] See the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

- Long-term follow-up studies may be required for GE products for the collection of data on delayed adverse reactions with GE products.[32]

Benefit-risk assessment

- A benefit-risk assessment will be based on the data collected, considering demonstrated benefits and adverse events, with consideration of the severity of the disease and patient tolerance for risk.

Post-marketing considerations

- FDA expects that the amount of safety data available at the time of approval for the products described in this guidance will be limited.

- As such, FDA will likely require a PMR or issue a PMC to provide additional safety information in the post marketing setting and take appropriate action should a safety signal be identified.

- If a product receives accelerated approval, a PMR will be issued to study the drug further to verify and describe its clinical benefit. FDA generally intends to require that the trial to verify and describe clinical benefit be underway prior to the accelerated approval action. FDA may also use expedited withdrawal authorities if, for example, the sponsor fails to conduct a confirmatory trial with due diligence or a confirmatory trial fails to verify and describe its clinical benefit, among other reasons.[33]

D. CMC

Manufacturing for investigational and approved drugs (including biological products) must comply with CGMP, as required by section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(a)(2)(B)). CMC development should evolve concurrently with clinical development. Given the shortened clinical investigation phase expected for individualized therapies, sponsors of therapies described in this guidance should consider the following CMC recommendations:

- In general, the production of an investigational drug product for use in a Phase 1 clinical trial is exempt from compliance with the regulations in 21 CFR Part

[32] See the guidance for industry *Long Term Follow-Up After Administration of Human Gene Therapy Products* (January 2020).
[33] Section 506(c)(3)(A) of the FD&C Act.

211.[34] This exemption generally applies to studies that are designed to establish basic safety, rather than efficacy of the drug product.

- The Draft Guidance for Sponsor-Investigators: IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations (December 2021)[35] proposes recommendations that would be applicable for the RNA-targeted therapies described in this document.

- Due to the limited number of subjects being treated in clinical trials to support approval, it is expected that CMC development will occur rapidly. The sequence, structures (e.g., various modifications, conjugations), stereochemistry, and other physicochemical characteristics critical to the performance of the product should be well-defined, confirmed, and controlled to ensure consistency, where applicable. To this end, multiple aspects of the commercial manufacturing process should be considered when developing the manufacturing process to support the initial IND (e.g. scale, validation, commercial feasibility, etc.). Prior knowledge should be leveraged to the extent possible to effectively develop robust manufacturing process and control strategies. Some specific examples include the following:

    - The use of prior manufacturing knowledge to establish a well-controlled manufacturing process for investigational product development.

    - The use of prior development experience to anticipate the best dosage form, route of administration, formulation (composition) selection, characterization of the product, and control of critical quality attributes.

- The manufacturing process to support an NDA or BLA must be appropriately validated.[36]

    - The use of prior knowledge can be leveraged to support process validation for example, process performance qualification from one product may be used to support manufacturing process validation of a similar product using the same manufacturing process at the same manufacturing site. Additionally, for GE products with drug product variants, CMC information can be leveraged between product variants.

[34] 21 CFR 210.2(c).
[35] When final, this guidance will represent FDA's current thinking on this topic.
[36] 21 CFR 211.100(a) and 211.110(a).

683 - Key principles on process validation can be found in several FDA
684 guidance documents.[37]
685
686 - Minimizing manufacturing changes can avoid the need for comprehensive
687 comparability studies.[38]
688
689 • In addition to having a validated manufacturing process, all assays used for
690 release and stability testing must comply with the relevant application-related and
691 CGMP regulations.[39]
692
693 - Analytical methods used for release testing in an NDA or BLA must be
694 validated.[40] Information on method validation can be found in several
695 FDA guidance documents.[41]
696
697 - Analytical methods that have already been qualified or validated for a
698 closely related product or product variant may be appropriate with a
699 suitability evaluation focused on product differences.
700
701 - For licensure of biological products, a potency assay as described in 21
702 CFR 610.10 is required.
703
704 ▪ Considerations for potency assays for GE products are described in
705 the Guidance for Industry: Human Gene Therapy Products
706 Incorporating Human Genome Editing (January 2024) and the
707 Draft Guidance for Industry: Potency Assurance for Cellular and
708 Gene Therapy Products (December 2023).[42]
709
710 ▪ For a GE product composed of drug product variants needed to
711 address different mutations, the potency assay should be designed
712 as a mutation-specific assay that can be adapted to address
713 different mutations.

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[37] See the guidance for industry *Process Validation: General Principles and Practices* (January 2011), the guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009), and the guidance for industry *Q11 Development and Manufacture of Drug Substances* (November 2012).
[38] See the draft guidance for industry *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products* (July 2023). When final, this guidance will represent the FDA's current thinking on this topic.
[39] See, for example, 21 CFR 610.10 (regarding tests for potency for biological products); 21 CFR 211.165(e) (regarding the establishment and documentation of the accuracy, sensitivity, specificity, and reproducibility of test methods); 21 CFR 211.160(b) (regarding laboratory controls); and 21 CFR 211.194(a)(2) (regarding laboratory records of testing methods).
[40] See, e.g., 21 CFR 211.110(a).
[41] See the guidances for industry *Q2(R2) Validation of Analytical Procedures* (March 2024) and *Q14 Analytical Procedure Development* (March 2024).
[42] When final, this guidance will represent the FDA's current thinking on this topic.

- Due to the limited number of batches expected to be manufactured, sponsors should develop a strategy for establishing a shelf life for the intended product early in development. This should include collecting stability data for all batches manufactured using appropriately validated and stability-indicating assays and investigating opportunities to leverage related product data to support and justify the proposed shelf life.

- Relevant information from other related products (e.g., similar products that have the same formulation or are administered using the same delivery device) can be leveraged to support in-use stability and delivery device compatibility in an IND, NDA or BLA.

FDA strongly recommends that sponsors discuss their CMC plans with the Agency early in product development.

E. Other Considerations

Importance of Data Sharing

- FDA strongly supports and encourages continued research in understanding how the role of an individualized therapy in rare genetic diseases can inform the successful development of effective treatments for broader rare genetic diseases.

- Shared learning through appropriate data sharing is one opportunity to facilitate continued research.

- Sponsors should consider incorporating language into the informed consent document, as appropriate, that would allow sharing participant data for future research.