Human Gene Therapy for Rare Diseases

Guidance for Industry

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I. INTRODUCTION

This guidance provides recommendations to sponsors developing human gene therapy (GT)\(^1\) products intended to treat a rare disease\(^2\) in adult and/or pediatric patients regarding the manufacturing, preclinical, and clinical trial design issues for all phases of the clinical development program. Such information is intended to assist sponsors in designing clinical development programs for such products, where there may be limited study population size and potential feasibility and safety issues, as well as issues relating to the interpretability of bioactivity/efficacy outcomes that may be unique to rare diseases or to the nature of the GT product itself. This guidance finalizes the draft guidance of the same title dated July 2018.

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.

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\(^1\) Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells. Gene therapy products meet the definition of “biological product” in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings (see Federal Register Notice: Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 FR 53248, October 14, 1993), [https://www.fda.gov/media/76647/download](https://www.fda.gov/media/76647/download)).

II. BACKGROUND

The National Institutes of Health (NIH) reports that nearly 7,000 rare diseases affect more than 25 million Americans. Approximately 80% of rare diseases are caused by a single-gene defect, and about half of all rare diseases affect children. Since most rare diseases have no approved therapies, there is a significant unmet need for effective treatments, and many rare diseases are serious or life-threatening conditions. As a general matter, developing safe and effective products to treat rare diseases can be challenging. For example, it might be more difficult to find and recruit patients with rare diseases into clinical trials. Additionally, patients may have highly diverse clinical manifestations and rates of disease progression that are difficult to predict. These challenges are also present for the development of GT products. However, despite these challenges, GT-related research and development in the area of rare diseases continues to grow at a rapid rate.

III. CONSIDERATIONS FOR CHEMISTRY, MANUFACTURING AND CONTROLS

The general chemistry, manufacturing and controls (CMC) considerations for product manufacturing, testing and release of GT products for rare diseases are the same as those described for other GT products (Ref. 1). However, some aspects of the development programs for rare diseases, such as limited population size and fewer lots manufactured, may make it challenging to follow traditional product development strategies. In traditional product development, critical quality attributes (CQAs) of the product are evaluated during each phase of clinical development, and characterization data from many drug product lots are correlated to clinical outcomes. Smaller study populations may result in the need for fewer manufacturing runs, which can make it difficult to establish the critical process parameters (CPP) necessary for ensuring CQAs. In addition, GT products may have CQAs with higher variability than drugs or well-characterized biologics, which can add to CQA uncertainty. However, demonstrating process control to ensure a consistent product with defined CQAs for potency, identity and purity is required to demonstrate compliance with licensure and regulatory requirements (Refs. 2 and 4).

These factors make it even more critical that a sponsor of a GT product for a rare disease establish a well-controlled manufacturing process along with suitable analytical assays to assess product CQAs for product concentration, potency, identity and purity as early in development as possible, optimally before administration of the GT product to the first subject (Refs. 2 and 3). When changes to the manufacturing process are necessary, a comparability assessment may be needed. Importantly, as the Phase 1 study may provide evidence of safety and effectiveness for licensure, we recommend that sponsors characterize the product’s CQAs, and implement manufacturing CPPs, before initiating clinical studies. Innovative strategies for understanding CQAs may include applying prior knowledge from other similar products, leveraging product characterization data from nonclinical studies, evaluating CPPs during engineering runs, or the production of multiple small lots versus a single large product lot. Sponsors developing GT products for rare diseases are strongly encouraged to contact the Office of Tissues and Advanced

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Therapies (OTAT) in the Center for Biologics Evaluation and Research (CBER) prior to investigational new drug application (IND) submission and during product development to discuss their product-specific considerations, which may include:

- **Product-related variations** may have a pronounced effect on the interpretability of clinical data in rare disease studies. Examples of product variations include impurities such as empty and wild-type viral particles in viral vectors, and variability in genetically-modified cell therapies caused by intrinsic differences among subject’s cells. Establishment of assays for characterization of product-related variants and impurities will be important for program success.

- **Potency assays** are critical to assess product functional activity, consistency and stability, and to provide evidence of comparability after changes to the manufacturing process. To better understand product function(s), we strongly encourage the evaluation of multiple product characteristics before initiating clinical studies. These characterization studies may in turn be used to establish a potency test, which is critical to successful product development. Therefore, we recommend that a potency test that measures a relevant biological activity be qualified for suitability (i.e., accuracy, precision, sensitivity, specificity) prior to conducting trials intended to provide substantial evidence of effectiveness for a marketing application and validated prior to licensure (Ref. 2).

- **It can be challenging** to develop and validate a manufacturing process or perform comparability studies and develop suitable assays to measure CQAs when there is limited availability of starting materials (e.g., autologous cells), a lack of reference materials, or limited process understanding (Ref. 3). Sponsors are encouraged to consider, where possible, implementing manufacturing changes needed for commercial-scale production and demonstrating product comparability prior to the initiation of clinical trials intended to provide substantial evidence of effectiveness for a marketing application. Importantly, if product comparability cannot be demonstrated, additional clinical data may be needed (Refs. 4 and 5).

### IV. CONSIDERATIONS FOR PRECLINICAL STUDIES

A preclinical program that is tailored to the investigational product and the planned early-phase clinical trial contributes to characterization of the product’s benefit/risk profile for the intended patient population. The overall objectives of a preclinical program for a GT product include: 1) identification of a biologically active dose range; 2) recommendations for an initial clinical dose level, dose-escalation schedule, and dosing regimen; 3) establishment of feasibility and reasonable safety of the proposed clinical route of administration (ROA); 4) support of patient eligibility criteria; and 5) identification of potential toxicities and physiologic parameters that help guide clinical monitoring for a particular investigational product. In addition, to justify conducting a pediatric first-in-human clinical trial that is associated with more than a minor increase over minimal risk, the preclinical program should include studies designed to demonstrate a prospect of direct benefit (21 CFR 50.52) of the investigational GT product (refer to section V.A. of this document for further discussion). Preclinical evidence of a prospect of
direct benefit is most important when clinical evidence of effectiveness is not available from adult subjects with the same disease.

Further details for general considerations in preclinical studies are available in a separate guidance document (Ref. 6). Although not specific to rare diseases, the following elements are recommended in the development of a preclinical program for an investigational GT product:

- Preclinical in vitro and in vivo proof-of-concept (POC) studies are recommended to establish feasibility and support the scientific rationale for administration of the investigational GT product in a clinical trial. Data derived from preclinical POC studies may guide the design of both the preclinical toxicology studies, as well as the early-phase clinical trials. The animal species and/or models selected should demonstrate a biological response to the investigational GT product that is similar to the expected response in humans.

- Biodistribution studies should be conducted to assess the distribution, persistence, and clearance of the vector from the site of administration to target and non-target tissues, including applicable biofluids (e.g., blood, lymph node fluid, cerebrospinal fluid (CSF)) as feasible. These data can determine extent of tissue transduction and transgene expression, evaluate whether expression is transient or persistent, and guide the design of the preclinical toxicology studies as well as the early-phase clinical trials (Refs. 6-8).

- Toxicology studies for an investigational GT product should incorporate elements of the planned clinical trial (e.g., dose range, ROA, dosing schedule, evaluation endpoints, etc.) to the extent feasible. Study designs should be sufficiently comprehensive to permit identification, characterization, and quantification of potential local and systemic toxicities, their onset (i.e., acute or delayed) and potential resolution, and the effect of dose level on these findings. In some cases, additional assessments may also be important to consider, such as safety and feasibility of the proposed GT delivery system and procedure, and immune response directed against the vector and the expressed transgene product.

- Additional nonclinical studies may be needed to address such factors as: 1) the potential for developmental and reproductive toxicity; and 2) significant changes in the manufacturing process or formulation that may impact comparability between the product administered in clinical trials and the product intended for licensure.

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4 The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. We support the principles of the “3Rs,” to reduce, refine, and replace animal use in testing when feasible. Proposals, with justification for any potential alternative approaches (e.g., in vitro or in silico testing), should be submitted during early communication meetings with FDA (see section VII of this document). We will consider if such an alternative method could be used in place of an animal test method.

V. CONSIDERATIONS FOR CLINICAL TRIALS

Many rare disorders are serious, with no approved treatments, and represent substantial unmet medical needs for patients. Because of phenotypic heterogeneity, disease manifestations are likely to vary in onset and severity. Information obtained from a natural history study can potentially provide critical information to guide every stage of drug development from drug discovery to determining effectiveness and safety of the drug in treating a disease (Ref. 9). If there is insufficient information on the natural history of the disease to inform the selection of a historical comparator or to inform clinical endpoint selection, additional natural history data may be needed (Ref. 10).

In a majority of these disorders, clinical manifestations appear early in life, and there are ethical and regulatory considerations regarding enrollment of children into clinical trials. These considerations should inform the design of both early- and late-phase clinical trials. Further details of general considerations for GT clinical trials are available in a separate guidance document (Ref. 11).

The following important elements are recommended for consideration during clinical development of investigational GT products intended for treatment of rare diseases (although they are not exclusively applicable to GT products for rare diseases).

A. Study Population

Selection of the study population should consider existing preclinical or clinical data to determine the potential risks and benefits for the study subjects. In addition, sponsors should consider whether the proposed study population is likely to provide informative safety and/or efficacy data (Ref. 11). The following points should be considered with respect to trials of GT products for rare diseases:

- If the disease is caused by a genetic defect, the sponsor should perform genetic test(s) for the specific defect(s) of interest in all clinical trial subjects. This information is important to ensure correct diagnosis of the disorder of interest. In addition, since many of these disorders can involve either deletions or functional mutations at any of several loci within a specific gene, safety and effectiveness may be linked to genotype in unpredictable ways. Given this, early understanding of such associations may help in planning future clinical trials. Therefore, if there are no readily available, reliable means of obtaining the needed genetic diagnosis, a companion diagnostic may be needed and therefore should be considered early in development (Ref. 12).

- Pre-existing antibodies to any component of the GT product may pose a potential risk to patient safety and limit its therapeutic potential. Antibodies to the gene therapeutic agent may also limit the potential for re-administration of the product.
Sponsors may choose to exclude patients with pre-existing antibodies to the GT product. In such cases, the sponsor should strongly consider contemporaneous development of a companion diagnostic to detect antibodies to the GT product. If an in vitro companion diagnostic is needed to appropriately select patients for study (and later, once the GT product is approved, for treatment), then submission of the marketing application for the companion diagnostic and submission of the biologics license application for the GT product should be coordinated to support contemporaneous marketing authorizations.

Severity of disease should be considered in designing clinical GT trials in the context of the ability to report and detect adverse events as well as considerations related to, the anticipated risk and potential benefits to subjects (Ref. 11). Subjects with severe or advanced disease might experience confounding adverse events that are related to the underlying disease rather than to the GT product itself. Subjects with earlier stages of disease may derive more benefit from the therapy.

It is important that clinical investigations in pediatric patients address ethical considerations for conducting investigations in vulnerable populations. FDA regulations at 21 CFR Part 50, Subpart D contain additional safeguards for children in clinical investigations. Clinical investigations involving no greater than minimal risk may involve children in accordance with 21 CFR 50.51. Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects may involve children as set forth in 21 CFR 50.52. An investigation involving greater than minimal risk and no prospect of direct benefit to individual subjects, but which is likely to yield generalizable knowledge about the disorder or condition, may involve children as set forth in 21 CFR 50.53, which includes, for example, a finding by the IRB that the risk represents a minor increase over minimal risk. FDA’s regulation at 21 CFR 50.54 also addresses clinical investigations not otherwise approvable and describes a process to follow to determine whether the investigation may involve children. In addition to the determinations required under applicable provisions of subpart D, adequate provisions must be made to obtain the permission of the parents and the assent of the child as described in 21 CFR 50.55.

The risks of most GT products include the possibility of unintended effects that may be permanent, along with adverse effects due to invasive procedures that may be necessary for product administration. Because of these risks, it is generally not acceptable to enroll normal, healthy volunteers into GT studies. A well-written informed consent document is also essential.
B. Study Design

For rare diseases, there may be a limited number of patients who may qualify for enrollment into a clinical study. As a result, it is often not feasible to enroll unique subjects for all studies conducted under different phases of the clinical development program. Limitation in the number of prospective subjects warrants the collection of as much pertinent data (e.g., adverse events, efficacy outcomes, biomarkers) as possible from every subject, starting from the first-in-human study. All such data may be valuable to inform the design of subsequent studies (e.g., selection of study populations and endpoints). Sponsors developing GT products for rare diseases should consider the following:

- The randomized, concurrent-controlled trial is generally considered the ideal standard for establishing effectiveness and providing treatment-related safety data. Randomization in early stages of development is encouraged.

- Sponsors should consider designing their first-in-human study to be an adequate and well-controlled investigation that has the potential, depending on the study results, to provide evidence of effectiveness to support a marketing application.

- Placebo controls, when feasible, are recommended to facilitate the interpretability of both safety and efficacy results. If a study has multiple dose-level cohorts, consider randomizing some subjects in each cohort to receive placebo.

- To promote interpretability of data for studies that enroll subjects with different disease stages or severities, it is important for sponsors, when applicable, to consider stratified randomization based on disease stage/severity.

- For some genetically targeted indications (e.g., a genetic skin disease), the use of an intra-subject control design may be useful. Such intra-subject comparisons avoid the problem of variability among subjects that occurs with inter-subject controls. Thus, intra-subject controls can facilitate the assessment of local therapeutic effects and are recommended for consideration when appropriate.

- A single-arm trial using historical controls, sometimes including an initial observation period, may be considered if there are feasibility issues with conducting a randomized, controlled trial.

- If a single-arm trial design with a historical control is necessary, then knowledge of the natural history of disease is critical. Natural history data may provide the basis of a historical control, but only if the control and treatment populations are adequately matched, in terms of demographics, concurrent treatment, disease state, and other relevant factors. In circumstances where randomized, concurrent-controlled trials cannot be conducted and the natural history is well characterized, sponsors may consider the clinical performance of available
therapies (if there are any) when setting the performance goal or criteria against which the product effect will be tested.

- A small sample size, together with high inter-subject variability in clinical course, diminishes a study’s power to detect treatment-related effects. Therefore, alternative trial designs and statistical techniques that maximize data from a small and potentially heterogeneous group of subjects (including genetic heterogeneity) should be considered. Ideally, an endpoint based on a treatment outcome that is not expected to occur spontaneously in the natural course of the disease can facilitate the interpretability of a small trial.

- Clinical protocols should include adequate measures to minimize bias. The preferred approach to minimize bias is to use a study design that includes blinding.

- Efforts should be made early in the GT product development program to identify relevant biomarkers and to leverage all scientifically relevant information from published investigations for the disease of interest (or related diseases), to the extent possible. Some biomarkers or endpoints are very closely linked to the underlying pathophysiology of the disease (e.g., a missing metabolite in a critical biosynthetic pathway). In this case, changes in such biomarkers could be used during drug development for dose-selection, or even as an early demonstration of drug activity.

- Regarding concomitant medication(s): In some situations, study subjects may continue to take their pre-study medication(s), particularly if medication discontinuation would pose substantial risks, and if use of such concomitant medication(s) would not interfere with the objectives of the trial. The dose of concomitant medication should be stable over a specific time period (e.g., until measurement of the primary endpoint), which should be justified in the clinical protocol.

C. Dose Selection

- Dose selection should be informed by all available sources of clinical information (e.g., publications, experience with similar products, experience in related patient populations).

- Leveraging non-human data obtained in animal models of disease and in vitro data may be, in some cases, the only way to estimate a starting human dose that is anticipated to provide benefit. Additional dosing information can be obtained from predictive models based on current understanding of in vitro enzyme

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6 Additional information on the biomarkers can be found at: https://www.fda.gov/drugs/cder-biomarker-qualification-program/biomarker-guidances-and-reference-materials.
kinetics (including characterizing the enzyme kinetics in relevant cell lines), and allometric scaling.

- For early-phase studies in subjects with serious or life-threatening diseases and an unmet medical need, study treatment should ideally start with a potentially therapeutic dose. However, dose exploration may be needed to identify an optimal therapeutic dose.

- If the transgene expression and consequent treatment effect decrease over time, consideration may be given to repeat administration of the GT product. Subjects given a GT product may experience an enhanced immune response with repeat administration. Assessment of immunogenicity and its clinical manifestations (loss of treatment effect and toxicity) are even more critical in the setting of repeat administration.

D. Safety Considerations

- Clinical trials should include a monitoring plan that is adequate to protect the safety of clinical trial subjects. The elements and procedures of the monitoring plan should be based upon the patient’s disease, what is known about the GT product, including dosing frequency (as applicable), preclinical toxicology, as well as CMC information, and, if available, previous human experience with the proposed product or related products (Ref. 11).

- Innate and adaptive immune responses directed against one or more components of GT products (e.g., against the vector and/or transgene) may impact product safety and efficacy. Early development of appropriate assays to measure product-directed immune responses may be critical to program success. Development of neutralizing and non-neutralizing immune responses that are directed against the product should be monitored throughout the clinical trial (Ref. 13).

- When there is limited previous human experience with a specific GT product, administration to several subjects concurrently may expose those subjects to unacceptable risk. Most first-in-human trials of GT products should stagger administration to consecutively enrolled subjects, for at least an initial group of subjects, followed by staggering between dose cohorts. This approach limits the number of subjects who might be exposed to an unanticipated safety risk (Ref. 11). The optimal dosing interval between consecutively enrolled subjects and dose cohorts should be discussed with OTAT prior to beginning the trial.

- Because of the unique nature of the mechanism of action involving genetic manipulation, a potential exists for serious long-term effects that may not be apparent during development or even at the time of an initial licensure. The long-term safety of GT products is currently unknown. The appropriate duration
of long-term follow-up depends on the results of preclinical studies with this product, knowledge of the disease process, and other scientific information (Ref. 7).

- Early-phase GT clinical trial protocols should generally include study stopping rules, which are criteria for halting the study based on an observed incidence of adverse events. The objective of study stopping rules is to limit subject exposure to risk in the event that safety concerns arise. Well-designed stopping rules may allow sponsors to assess and address risks identified as the trial proceeds, and to amend the protocol to mitigate such risks and to assure that human subjects are not exposed to unreasonable and significant risk of illness or injury.

- The potential for viral shedding should be addressed early in product development (Ref. 14).

- Pharmacovigilance systems should actively monitor each recipient of a GT product (Refs. 7 and 15).

E. Efficacy Endpoints

Demonstration of clinical benefit of a GT product follows the same principles as for any other product. However, in some cases there may be unique characteristics of GT products (e.g., a protein that is expressed by a GT product may have different bioactivity than standard enzyme replacement therapy) that warrant additional considerations both pre-approval and post-marketing. Prior to commencing clinical trials of GT products for rare diseases, it is critically important to have a discussion with FDA about the primary efficacy endpoint(s). For many rare diseases, well-established, disease-specific efficacy endpoints are not available (Ref. 16). Endpoint selection for a clinical trial of a GT product for a rare disease should consider the following:

- Sponsors should understand the pathophysiology and natural history of a disease as fully as possible at the outset of product development. Full understanding of mechanism of product action is not required for marketing approval; however, understanding of disease pathophysiology is important in designing clinical trials, including selection of endpoints.

- Sponsors may consider seeking accelerated approval of a GT product for a rare disease pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) based on a surrogate endpoint.7 Understanding disease

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7 According to section 507(e)(9) of the FD&C Act [21 USC 357(e)(9)] “[t]he term ‘surrogate endpoint’ means a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, and—

(A) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or

(B) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product in accordance with section 506(c).
Contains Nonbinding Recommendations

Pathophysiology and natural history can help identify potential surrogate endpoints that are reasonably likely to predict clinical benefit. To support accelerated approval, the sponsor should provide sufficient data to support a conclusion that the proposed endpoint is reasonably likely to predict clinical benefit. In general, such data should, at a minimum, demonstrate a correlation between changes in the proposed surrogate endpoint and a beneficial clinical effect.

- Sponsors should identify specific aspects of the disease that are meaningful to the patient and might also be affected by the GT product’s activity (Ref. 17).

- Considerable information can be gained by collecting clinical measurements repeatedly over time. Such a longitudinal profile allows the assessments of effect, largely based on within-patient changes, that otherwise could not be studied.

F. Patient Experience

Patient experience data⁸ may provide important additional information about the clinical benefit of a GT product. FDA encourages sponsors to collect patient experience data during product development, and to submit such data in the marketing application.

VI. EXPEDITED PROGRAMS

There are several programs that may be available to sponsors of GTs intended to address unmet medical needs in the treatment of serious or life-threatening conditions. These programs, including regenerative medicine advanced therapy designation, breakthrough therapy designation, fast track designation, accelerated approval, and priority review, are intended to facilitate and expedite development and review of these therapies. For example, regenerative medicine advanced therapy designation and breakthrough therapy designation call for increased FDA attention to these potentially promising therapies, offering sponsors more frequent interactions with FDA on efficient trial design and overall drug development. Further information on these expedited programs is available in separate guidance documents (Refs. 18 and 19).

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⁸ As defined in section 569(c) of the FD&C Act, [21 USC 360bbb-8c], the term “patient experience data” includes data that are:

- Collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and

- Intended to provide information about patients’ experiences with a disease or condition, including the impact (including physical and psychosocial impacts) of such disease or condition, or a related therapy or clinical investigation, on patients’ lives; and patient preferences with respect to treatment of such disease or condition.

VII. COMMUNICATION WITH FDA

FDA recommends communication with OTAT early in product development, before submission of an investigational new drug application (IND). There are different meeting types that can be used for such discussions, depending on the stage of product development and the issues to be considered. These include pre-IND meetings prior to submission of the IND (Ref. 20), and INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings, which can be used earlier in development to discuss issues such as preclinical development or manufacturing, so that the sponsor can obtain non-binding regulatory advice.9

9 Going forward, INTERACT meetings will serve in place of pre-pre-IND meetings. For additional information about INTERACT meetings, please see https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings-initial-targeted-engagement-regulatory-advice-cber-products.
VIII. REFERENCES


14. Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products; Guidance for Industry, August 2015. [https://www.fda.gov/media/89036/download](https://www.fda.gov/media/89036/download).
Contains Nonbinding Recommendations


*When finalized, this guidance will represent FDA’s current thinking on this topic.