Human Gene Therapy for Rare Diseases

Draft Guidance for Industry

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HUMAN GENE THERAPY FOR RARE DISEASES

DRAFT GUIDANCE FOR INDUSTRY

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I. INTRODUCTION

This guidance provides recommendations to stakeholders developing a human gene therapy (GT) product\(^1\) 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.

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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. Human gene therapy products are defined as 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, genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing (Ref. 1), 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.

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, many rare diseases exhibit a number of variations or sub-types. Consequently, patients may have highly diverse clinical manifestations and rates of disease progression with unpredictable clinical courses. 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 PRODUCT DEVELOPMENT

The general chemistry, manufacturing and control (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. 2). 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 (CQA) of the product are evaluated during each phase of clinical development, and characterization data from many product lots are correlated to clinical outcomes. In addition, GT products may have CQA with higher variability than drugs or well-characterized biologics, which can add to CQA uncertainty. 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 CQA. However, demonstrating process control to ensure a consistent product with predefined CQA for potency, identity and purity is required to demonstrate compliance with licensure and regulatory requirements.3

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 CQA as early in development as possible, optimally before administration of the GT product to the first subject. Importantly, as the phase 1 study may provide evidence of safety and effectiveness, characterization of product CQA and manufacturing CPP should be implemented during early clinical development, and innovative strategies such as the production of multiple small lots versus a single large product lot may be considered. Sponsors developing GT products for rare diseases are strongly encouraged to contact the Office of Tissues and Advanced

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

- Product-related variations, including those contributed by intrinsic differences among subjects’ cells, may have a more pronounced effect on the interpretability of smaller rare disease studies. This is equally true of impurities such as empty and wild type viral particles that may be present in viral vectors. 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, stability, and to provide evidence of comparability after changes to the manufacturing process. Therefore, we strongly encourage the evaluation of multiple product characteristics that could be used to establish a potency test during initial clinical studies. As these assays are critical to product development, we recommend that a potency test that measures a relevant biological activity be qualified for suitability (i.e., accurate, precise, sensitive, specific) prior to conducting trials intended to provide substantial evidence of effectiveness for a marketing application, and validated for licensure (Ref. 3).

- Limited availability of starting materials (e.g., autologous cells) and reference materials to design suitable assays to measure CQA, as well as limited process understanding, can hamper manufacturing process development, comparability studies, and process validation (Ref. 4). 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 studies may be needed.

IV. CONSIDERATIONS FOR PRECLINICAL STUDIES

A preclinical program that is tailored to the investigational product and 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 first-in-human clinical trial in pediatric subjects 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 50.53) of the investigational GT product (refer to section V.A. of this document for further discussion). This objective is important when clinical evidence 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. 5). 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 can 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 pharmacokinetic (PK) profile of a GT product (Ref. 6). These data encompass the distribution profile of the vector from the site of administration to target and non-target tissues, including biofluids (e.g., blood, lymph node fluid, cerebrospinal fluid (CSF)) as applicable. 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.

- Toxicology studies for an investigational GT product should incorporate the 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 mitigation and 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 vector and expressed transgene product.

- The conduct of additional nonclinical studies\(^4\) 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.

\(^4\) The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design, to maximize the contribution and predictive value of the resulting data for clinical safety and therapeutic activity. We encourage sponsors to explore opportunities for reducing, refining, and replacing animal use in the preclinical program. For example, it may be appropriate to use *in vitro* or *in silico* testing to complement or replace animal studies. Sponsors are encouraged to submit proposals and justify any potential alternative approaches, which we will evaluate for equivalency to animal studies.
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. 7). However, there may be insufficient information on the natural history of the disease to inform the selection of a historical comparator or to inform clinical endpoint selection in future clinical trials.

In a majority of these disorders, clinical manifestations appear early in life, and there are ethical and regulatory considerations regarding enrollment of children in clinical trials. These considerations should factor into 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. 8).

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. 8). 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.

- Pre-existing antibody to the GT product may limit its therapeutic potential. 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 (Ref. 8), as well as the anticipated risk and potential benefits to subjects. 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; however, they may be more willing to accept the risk of an investigational GT product in the context of the anticipated clinical benefit.

- Since most rare diseases are pediatric diseases or have onset of manifestations in childhood, pediatric studies are a critical part of drug development. However, treatment in pediatric patients cannot proceed without addressing ethical considerations for conducting investigations in vulnerable populations. Unless the risks of an investigational drug are no more than a minor increase over minimal risk (21 CFR 50.53), the administration of an investigational drug in children must offer a prospect of direct clinical benefit to individually enrolled patients, the risk must be justified by the anticipated benefit, and the anticipated risk-benefit profile must be at least as favorable as that presented by accepted alternative treatments (21 CFR 50.52). Additionally, adequate provisions must be made to obtain the permission of the parents and the assent of the child as per 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 strongly encouraged when feasible.

- 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.

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

- For some GT indications (e.g., a genetic skin disease), the use of an intra-subject control design may be useful. Comparisons of local therapeutic effects can be facilitated by the elimination of variability among subjects in inter-subject designs.

- 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 use of a type of 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 should be considered. Ideally, utilizing as an endpoint a treatment outcome that virtually never occurs in the natural course of the disease would greatly facilitate the design and cogency of small trials.
Adequate measures to minimize bias should be undertaken. The preferred approach to minimize bias is to use a study design that includes blinding.

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 kinetics (including characterizing the enzyme kinetics in relevant cell lines), and allometric scaling.

- For early-phase studies, clinical development of GT products should include evaluation of two or more dose levels to help identify the potentially therapeutic dose(s). Ideally, placebo controls should be added to each dose cohort.

- Some GT products may have an extended duration of activity, so that repeated dosing may not be an acceptable risk until there is a preliminary understanding of the product’s toxicity and duration of activity.

Efforts should be made early in the GT product development program to identify and validate biomarkers and to leverage all available information from published investigations for the disease of interest (or related diseases). 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, total or substantial restoration of the biosynthetic metabolic pathway may generally be expected to confer clinical benefit. Changes in such biomarkers could be used during drug development for dose-selection, or even as an early demonstration of drug activity.

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 what is known about the GT product, including preclinical toxicology, as well as CMC information, and, if available, previous human experience with the proposed product or related products (Ref. 8).

- 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. 9).

- 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. 8).
The optimal dosing interval between consecutively enrolled subjects and dose
cohorts should be discussed with OTAT prior to conduct of 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. 6).

- Early-phase GT clinical trial protocols should generally include study stopping
rules, which are criteria for halting the study based on the observed incidence of
particular 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 or 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. 10).

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. 11). Endpoint selection for a clinical trial of a GT
product for a rare disease should consider the following:
Sponsors should utilize an understanding 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 product approval; however, understanding of pathophysiology is important in planning clinical trials, including selection of endpoints.

For sponsors that are considering 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, it will be particularly important to understand the pathophysiology and natural history of the disease in order to help identify potential surrogate endpoints that are reasonably likely to predict clinical benefit.

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. 12).

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

F. Patient Experience

Patient experience data\(^5\) 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 that are intended to facilitate and expedite development and review of these therapies, including regenerative medicine advanced therapy designation, breakthrough therapy designation, fast track designation, accelerated approval, and priority review. In particular, regenerative medicine advanced therapy designation and breakthrough therapy designation call for earlier attention.

\(^5\) As defined in section 569(c) of the FD&C Act, 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.

Additional information on Patient-Focused Drug Development can be found on this website: https://www.fda.gov/drugs/developmentapprovalprocess/ucm579400.htm
from FDA to these potentially promising therapies, offering sponsors earlier and more frequent interactions with FDA on efficient trial design and overall drug development. Further information on these programs is available in separate guidance documents\textsuperscript{6,7}.

VII. COMMUNICATION WITH FDA

FDA recommends communication with OTAT early in product development, before submission of an 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 and, earlier in development, INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings\textsuperscript{8}. Early nonbinding, regulatory advice can be obtained from OTAT through an INTERACT meeting, which can be used to discuss issues such as a product’s early preclinical program, and/or through a pre-IND meeting prior to submission of the IND (Ref. 13).


\textsuperscript{8} Going forward, INTERACT meetings will serve in place of pre-pre-IND meetings. For additional information about INTERACT meetings, please see \url{https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm}.
VIII. REFERENCES


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