Human Gene Therapy for Hemophilia

Draft Guidance for Industry

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U.S. Department of Health and Human Services
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I. INTRODUCTION

This guidance is intended to assist stakeholders developing human gene therapy (GT)[1] products for the treatment of hemophilia. This guidance provides recommendations on the clinical trial design and related development of coagulation factor VIII (hemophilia A) and IX (hemophilia B) activity assays, including how to address discrepancies in factor VIII and factor IX activity assays. This guidance also includes recommendations regarding preclinical considerations to support development of GT products for the treatment of hemophilia. Additional clinical and preclinical recommendations are available through several other guidances.[2,3] This guidance does not provide recommendations for products for the treatment of hemophilia C (factor XI deficiency) or for the treatment of any bleeding disorders other than hemophilia A and B, because of the unique nature of those other bleeding disorders.

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.

[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.

[2] Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products, dated June 2015 https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf

[3] Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products, dated November 2013 https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf

The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Hemophilia therapy in the United States has progressed from replacement therapies for on-demand treatment of bleeding to prophylaxis to reduce the frequency of bleeding. Current replacement therapies utilize plasma-derived coagulation factor or recombinant factor concentrates. Prophylaxis has been shown to prevent joint damage in children and allows lower factor usage compared to on-demand therapy, and is currently the optimal treatment for hemophilia. Dosing intervals with prophylaxis are associated with peaks and troughs and aim at maintaining trough levels >1% between doses. Compliance with dosing is a necessary aspect of prophylaxis, and patients may experience breakthrough bleeding episodes that require treatment with replacement therapies for control of bleeding. The main adverse event associated with factor replacement therapy is the development of inhibitors (neutralizing antibodies) to factor VIII or factor IX, which requires use of alternative therapies to overcome the effect of the inhibitor.

GT products for the treatment of hemophilia are being developed as single-dose treatments that may provide long-term expression of the missing or abnormal coagulation factor in the patient at steady levels to reduce or eliminate the need for exogenous factor replacement. GT products in the advanced phase of clinical development may use a vector to deliver the coagulation factor gene to the liver. The coagulation factor that is expressed may be different from the wild type (normal) form. For example, the coagulation factor may be a truncated variant, such as B domain-deleted factor VIII, or a hyper-functional natural variant (such as the Padua variant of factor IX).

III. CONSIDERATIONS FOR PRODUCT DEVELOPMENT

The general chemistry, manufacturing and control (CMC) considerations for product manufacturing, testing and release of GT products for the treatment of hemophilia are the same as those described for other GT products (Ref. 2). For early-phase clinical trials, a sponsor should be able to evaluate the identity, purity, quality, dose, and safety of a GT product. A potency assay to assess the biological activity of the final product, with relevant lot release specifications, should be established prior to the initiation of clinical trials intended to provide substantial evidence of effectiveness for a marketing application. To support licensure of a GT product, manufacturing processes and all testing methods for product release must be validated (21 CFR 211.165(e)). Sponsors developing GT products for hemophilia are strongly encouraged to contact the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research (CBER) early in product development to discuss product-specific issues.

IV. CONSIDERATIONS FOR FACTOR VIII/FACTOR IX ACTIVITY MEASUREMENTS ASSESSED BY DIFFERENT CLINICAL LABORATORY ASSAYS

One stage clotting (OC) assays and chromogenic (CS) assays have been used to measure factor activity; however, discrepancies in factor activity measurements between the OC and CS methods have been observed (Refs. 3-9). For example, in patients with hemophilia A treated with recombinant B-domain-deleted factor VIII products, CS assays indicate higher factor activity than OC assays. In contrast, for patients with hemophilia A who receive GT products that express a B-domain-deleted factor VIII transgene, OC assays indicate higher factor activity than CS assays. These contrasting results prevent us from generalizing our previous experience with recombinant factor VIII products to clinical benefits related to factor VIII levels produced by recipients of GT products. Similarly, for hemophilia B patients who receive GT products that express the Padua variant of factor IX, discrepancies between results of the OC and CS assays have been observed across products.

Factor activity assay discrepancies are not limited to differences between OC and CS assays, but are also observed between OC assays using different OC reagents. These discrepancies indicate structural and functional differences between the transgene proteins and normal factor proteins used as an assay standard. The discrepancies preclude reliable interpretation of factor activity measurements and present a challenge when factor activity levels are proposed as surrogate endpoints for hemostatic efficacy. Even if factor activity is not used as a surrogate endpoint to support accelerated approval, safe clinical management of patients in GT trials depends on an understanding of any assay discrepancies.

To better interpret these results, we recommend that sponsors consider:

- Performing animal or in vitro preclinical studies that compare the performance of OC and CS assays. Both assays should be calibrated in International Units (IU) of factor activity and should use a reference standard analogous to the expressed transgene, if available.[4]

- Using various clinical laboratory assays in preclinical animal studies and, where feasible, assays intended for human use.

We also recommend that sponsors perform analytical studies to clarify the biochemical root-causes for any discrepancies observed, addressing:

- Methodology (OC vs. CS)

[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.

- Reagents (phospholipids, activators, chromogenic substrates)
- Conditions (incubation times, temperature)
- Choice of reference standards
- Vendors/kits/lab being used
- Correlations between factor activity and antigen levels (by immunoassay)

Data from preclinical studies should inform the selection of assays used in early-phase clinical studies to:

- Measure factor activity intended to be used as a surrogate endpoint to support accelerated approval; and
- Guide exogenous replacement therapy for the treatment of bleeding.

During clinical trials, we recommend that sponsors consider:

- Performing a comparative field study with patient plasma samples using assays routinely performed in clinical laboratories to evaluate the range of discrepancies.
- Performing bridging studies on patient samples if changes to the assay(s) are initiated after a clinical trial is underway.

V. 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.

Further details for general considerations in preclinical studies are available in a separate guidance document.[5] The following elements are recommended for consideration when

[5] Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products, dated November 2013 https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf

developing a preclinical program for an investigational GT product for treatment of hemophilia (some of which are not necessarily exclusive to GT products for treatment of hemophilia).

- 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. Several hemophilia animal models are available in the literature (Ref. 10) and can be used to demonstrate biological activity of an investigational GT product and to help the evaluation of the human response.

- Biodistribution studies are conducted to assess the pharmacokinetic (PK) profile of a GT product. (Ref. 11) These data encompass the distribution, persistence, and clearance of the vector and possibly the expressed transgene product in vivo, from the site of administration to target and non-target tissues, including biofluids (e.g., blood, lymph node fluid). 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 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.

- To support translation of effective and safe dose levels determined in preclinical studies to clinical trials, the assay for vector titer determination of the preclinical lots should be identical to the assay used for clinical lots. The assays for measuring factor activity in animals administered the GT product should be consistent to the assays used in humans. The factor activity assays are discussed in detail under section IV. of this document.

- As the clinical development program for an investigational GT product progresses to late-phase clinical trials and possible marketing approval, additional nonclinical studies may need to be considered to address: 1) the potential for reproductive/developmental toxicity and 2) any significant changes in the product manufacturing process or formulation changes for which product comparability may be an issue.

VI. CONSIDERATIONS FOR CLINICAL TRIALS

The fundamental considerations for clinical development programs of GT products for hemophilia are similar to those for other biologic products. Early-phase trials of GT products should not only evaluate safety and feasibility, but also gauge bioactivity and preliminary efficacy. Sponsors should evaluate the discrepancies between OC and CS assays early in the course of clinical development, prior to considering whether to pursue accelerated approval

using factor activity levels as a surrogate endpoint. Later-phase trials should be designed as adequate and well-controlled studiesthat can provide substantial evidence of effectiveness to support an application for marketing. For further details of general considerations for gene therapy clinical trials, please refer to relevant FDA guidance documents.[6, 7]

With respect to late-phase clinical trials that are intended to form the primary basis of an effectiveness claim for hemophilia GT products, we have the following recommendations:

A. Efficacy Endpoints

Sponsors may consider using the following efficacy endpoints as primary endpoints in clinical trials of GT products for hemophilia:

1. Traditional Approval

   - Annualized Bleeding Rate (ABR) as a primary endpoint to demonstrate clinical benefit.

2. Accelerated Approval

   - Factor activity may be considered as a surrogate endpoint[8] for primary efficacy assessment under the accelerated approval pathway.[9] (Ref. 12)

[6] Long Term Follow-Up After Administration of Human Gene Therapy Products: Draft Guidance for Industry, July 2018, (when finalized), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610797.pdf

[7] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, dated May 1998, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf

[8] For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a measure of clinical benefit, but is considered reasonably likely to predict clinical benefit.

[9] Section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 CFR Part 314, Subpart H – Accelerated Approval of New Drugs for Serious and Life Threatening Illnesses; 21 CFR Part 601, Subpart E.

However, to support the use of this surrogate endpoint, we recommend that you:

- Resolve discrepancies in factor assay results from various assay methods prior to considering a target factor activity as a surrogate endpoint for primary efficacy assessment.
- Determine a target factor activity level within the range of factor activity of normal population.

B. Study Design

While designing the clinical study, sponsors should consider the following pre-and post-administration recommendations:

1. Pre-administration Considerations

   We recommend:

   - Enrolling patients who have not required dose adjustments to their prophylactic replacement therapy for at least 12 months as this may best facilitate efficacy determinations following administration.
   - Observing patients for 6 months (lead-in period) in-study to collect data for ABR rates. ABR rates based on retrospective data collection from medical records may be subject to recall bias and missing information. Collecting:
     - ABR on an optimized prophylactic regimen to allow for within-subject (paired) comparison, increasing the statistical power relative to a design with parallel control.
     - Data for supportive endpoints (e.g., utilization of exogeneous replacement therapy or trough levels of factor activity).
   - Enrolling patients who use on-demand therapy prior to study entry in a separate cohort. Analysis of efficacy in this cohort may provide evidence to support the primary endpoint results.

2. Post-administration Considerations

   We recommend:

   - Using the same exogenous replacement therapy as in the lead-in phase to prevent (or treat) bleeding during the interval from post-GT product administration to steady state factor levels.
   - Including a washout period following exogenous factor replacement therapy to measure factor activity.

- Including a pre-specified target factor activity level or duration from treatment that specifies the timing to discontinue exogeneous factor prophylaxis.
- Specifying when assessment of ABR rates and durability of response is to begin (e.g., 3 weeks after steady state levels of factor activity is reached and exogenous factor prophylaxis is discontinued).
- Collecting data for analyses of supportive endpoints as related to the pre-treatment phase.
- Including a plan for initiation, dosing and tapering of corticosteroids for management (treatment or prophylaxis) of immune-mediated liver dysfunction.
- Including an assessment plan to correlate factor activity and bleeding rates.

C. Study Population

Sponsors may consider the following recommendations when identifying the target population:

- Pre-existing antibodies to the GT product may block delivery of the coagulation factor gene to its target (e.g., liver cells), limiting its therapeutic potential. Therefore, 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. (Ref. 13) 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. In addition, the clinical development plan should include studies to assess the effect of such pre-existing antibodies on the safety and efficacy of the product.
- Hemophilia affects both children and adults. Since many similar 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.

D. Statistical Considerations

To support a marketing application for traditional approval, we recommend a non-inferiority (NI) clinical trial design with ABR as the primary efficacy endpoint using a within-subject comparison design. We also recommend:

- Developing a NI margin (*M*) for comparing ABR of the investigational GT product to that of current prophylaxis therapies in the within-subject comparison trial.

- Proposing a statistical test to rule out that the ABR of the investigational GT product is more than *M* above the ABR of the within-subject comparator, taking into account the paired nature of the ABRs before and after GT for the same subject. One possible approach is to take the difference of each pair of ABRs, and then test that the median of the differences is less than *M* using the Wilcoxon Signed Rank test. We recommend that you also report a 95% confidence interval (CI) on the median of the ABR difference.

The within-subject comparison design provides an added advantage in evaluating the treatment effect of the investigational product by controlling for other factors that may also influence the bleeding outcomes. Additional information on general statistical and clinical considerations for these trials is described in FDA's guidance.[10]

E. Study Monitoring

The goal of the follow-up is to monitor the safety and durability of response. Sponsors may consider the following recommendations for short-term and long-term monitoring:

1. Short-Term Monitoring (first 2 years following GT product administration)

   We recommend:

   - Monitoring factor activity levels and liver function once or twice weekly in the interval between administration of the GT product and until steady state factor levels are reached.

   - Decreasing the frequency of monitoring of factor activity once steady state levels are achieved (for instance, monthly).

   - Periodic monitoring for levels of vector-related antibodies and assessing interferon-γ secretion from peripheral blood mononuclear cells by ELISPOT assay (more frequent monitoring may be appropriate if immune-mediated hepatic dysfunction is suspected).

[10] Non-Inferiority Clinical Trials to Establish Effectiveness; Guidance for Industry, dated November 2016, https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf

- Monitoring for inhibitor antibodies to factor VIII or factor IX.

- Assessing for viral shedding for products where a viral vector is used for gene transfer. (Ref. 15)

2. Long-Term Monitoring (≥2 years following GT product administration)

   We recommend:

   - Monitoring for adverse events for at least 5 years after exposure to non-integrating GT products and 15 years for integrating GT products. (Ref. 16)

   - Monitoring for adverse events to include: eliciting history of and non-invasive screening for hepatic malignancies; physical examination; and laboratory testing for hepatic function.

   - Monitoring for inhibitor antibodies to factor VIII or factor IX.

   - Monitoring for the emergence of new clinical conditions, including new malignancies and new incidence or exacerbation of pre-existing neurologic, rheumatologic, or autoimmune disorders.

   - Monitoring factor activity at least once every 6 months for 5 years.

F. Patient Experience

Patient experience data[11] 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.

The treatment landscape for hemophilia is evolving. Therefore, the benefit-risk profile of the investigational product will be evaluated in the context of the treatment landscape at the time of our review of a marketing application.

[11] 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

VII. 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 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.[12,13]

VIII. 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 and, earlier in development, INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings.[14]

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. 17)

[12] Guidance for Industry; Expedited Programs for Serious Conditions – Drugs and Biologics, dated May 2014, https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

[13] Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Draft Guidance for Industry, dated November 2017, when finalized, https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585414.pdf

[14] 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/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm

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