Human Gene Therapy for Hemophilia

Guidance for Industry

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance provides recommendations to sponsors developing human gene therapy (GT)[1]products for the treatment of hemophilia including 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 in other guidances (Refs. 1 and 2). 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 bleeding disorders. This guidance finalizes the draft guidance of the same title dated July 2018.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.

[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).

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. Routine prophylaxis is currently the optimal treatment strategy for hemophilia. Compliance with dosing is critical for effective prophylaxis, and dosing intervals aim to maintain trough levels >1% between doses. Patients on prophylaxis 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 the administered factor (VIII or IX), which then requires use of alternative therapies to overcome the effect of the inhibitor. The marketing approvals of factor VIII and factor IX replacement products currently indicated for prophylaxis were based on clinical trials with reduction of the annualized bleeding rate as the primary efficacy endpoint.

GT products for the treatment of hemophilia are being developed as single-dose treatments that may provide long-term expression of the deficient coagulation factor at steady levels to reduce or eliminate the need for exogenous factor replacement. GT products currently in 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 CHEMISTRY, MANUFACTURING AND CONTROLS

The general chemistry, manufacturing and controls (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. 3). 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 GT 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 (Ref. 4). 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 substrate (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. 5-11). 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 pose challenges in 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 hinder 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 factor activity, we, FDA, recommend that sponsors also consider:

- Performing in vitro studies using samples containing the transgene product from animal plasma or ex vivo-transduced cells to 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.

- Using various clinical factor activity 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)

- 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)

In early-phase clinical studies, interpretation of factor activity can be particularly challenging because the magnitude of discrepancies using different assays is not yet established for patient samples. Initially, data from in vitro factor assay studies using samples containing the transgene product from animal plasma or ex vivo-transduced cells may predict assay discrepancy in patient plasma. Patient samples collected during early-phase studies can clarify the actual range of discrepancies between factor activity values in GT patients. This assay discrepancy information should be obtained as early as possible if the assay is proposed to:

- Measure factor activity intended 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:

- Perform a comparative field study[2] with patient plasma samples using assays routinely performed in clinical laboratories to evaluate the range of discrepancies

- Perform bridging studies on patient samples if changes to the assay(s) are initiated after a clinical trial is underway.

- For GT products for hemophilia that express a variant protein with specific activity that deviates from normal, consider developing dedicated activity and antigen assays for the variant protein. Calibrate the factor activity and antigen assay standards for the variant proteins with the coagulation factor International Standards, as well as with the plasma samples obtained from normal healthy donors (Ref. 12).[3]

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

[2] For additional information on comparative field studies, please see references 5-11.

[3] The specific activity (i.e., ratio of factor activity to factor antigen of the variant proteins) may differ from that of normal coagulation factor proteins. The activity assay may be used to measure factor activity as a surrogate endpoint, and the factor antigen assay may be used to measure the level of protein expression.

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 (Ref. 2). The following elements are recommended in the development of a preclinical program for an investigational GT product for treatment of hemophilia. [4]

- 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 animal models of hemophilia (Ref. 13) can be used to demonstrate biological activity of an investigational GT product.

- Biodistribution studies should be conducted to assess 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 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. 2, 14, and 15).

- 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 use the same methodology as that 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

[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 VIII of this document). We will consider if such an alternative method could be used in place of an animal test method.

toxicity[5] 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 studies that can provide substantial evidence of effectiveness to support a BLA. For further details of general considerations for GT clinical trials, please refer to relevant FDA guidance documents (Refs. 14 and 16).

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

Approval of GT products could be based on factor activity levels, if scientifically justified. Our ability to use factor activity levels as validated surrogate endpoints that could support traditional approval, however, is currently limited by several scientific considerations. One of these considerations is that discrepant results may be obtained when using conventional factor assay methodology to assess the plasma factor levels in patients treated with GT products in comparison to the assessment of levels following the administration of their recombinant or plasma-derived counterparts. Another consideration is the lack of molecular characterization of the protein translated in vivo (e.g., factor VIII produced by hepatocytes), in contrast to recombinant factor concentrate products produced in vitro. Additional uncertainty exists regarding the extent of clinical benefit introduced by genetically engineered modifications that increase the specific activity of coagulation factor protein (e.g., factor IX Padua constructs). Thus, we recommend that sponsors seeking accelerated approval based on factor activity levels provide evidence, specific to their GT product, that correlates the factor levels with relevant clinical outcomes (e.g., through long term observation of patients exposed to the GT product in early stage clinical trials). We may consider revising these recommendations following the development of reliable evidence on correlates between factor activity and clinical benefit, when such evidence can be generalized to multiple GT products.

[5] For additional information on developmental and reproductive toxicity, please see section III.B. of the Preclinical Assessment of Investigational Cellular and Gene Therapy Products; Guidance for Industry, November 2013, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preclinical-assessment-investigational-cellular-and-gene-therapy-products.

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

1. Traditional Approval

Historically, applicants of products approved for treatment of hemophilia, (e.g., plasma-derived, recombinant replacement factors; bi-specific antibodies) have relied on annualized bleeding rate (ABR) to demonstrate clinical benefit. Although ABR is a direct assessment of clinical benefit, ABR has limitations in that it is a relatively infrequent event in patients on prophylactic factor regimens and the decision by a patient to treat a possible bleeding episode is usually somewhat subjective. For these reasons, more objective endpoints, such as factor activity levels, are desirable.

In the drug development process, validated surrogate endpoints may be used to obtain traditional approval for products. However, as noted above, at the present time factor activity levels have limitations that make it difficult for them to be used as a validated surrogate endpoint. To consider factor activity level as a validated surrogate endpoint, clinical data to assess and quantitate the relationship between steady-state factor activity levels and bleeding outcomes in patients with severe hemophilia are critical. One proposed approach to quantify such a relationship is to generalize factor activity levels observed in patients with mild phenotypes to predict factor activity levels that improve bleeding outcomes in patients with more severe phenotypes. However, factor activity assay discrepancies (section IV), transgene products with enhanced factor activity, and uncertainties regarding the applicability of extrapolation of factor activity levels in milder phenotypes to more severe phenotypes hinder such an approach. As data from ongoing clinical studies to assess and quantitate the relationship between steady-state factor activity levels and bleeding outcomes become available, along with reliable calibration methods for factor activity assays, FDA is optimistic that factor activity levels could potentially serve as a validated surrogate endpoint. Pending the availability of such data and reliable calibration methods, we recommend ABR as a primary endpoint to demonstrate clinical benefit.

2. Accelerated Approval

- Factor activity may be considered as a surrogate endpoint[6] for primary efficacy assessment under the accelerated approval pathway[7] (Ref. 17).

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

[6] 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).

[7] Section 506(c) of the 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.

- Conduct root-cause analyses to evaluate and explain discrepancies in factor assay results obtained from the various assay methods. If discrepancies are unresolved after addressing issues identified in the root-cause analyses, propose and justify a specific assay and target factor activity level as a surrogate endpoint for Agency consideration.
- Determine a target factor activity level for your product that predicts clinically meaningful hemostatic outcomes. Functional and structural differences between the transgene and normal factor protein may present a challenge in understanding the relationship between numerically identical factor activity levels or levels that are within the normal range[8] for the transgene protein and normal factor protein. In general, we expect that clinical study data will be necessary to support that any proposed target factor activity level is likely to predict a clinically meaningful hemostatic outcome. We intend to consider the determination of whether a specific hemostatic outcome is clinically meaningful in the context of available therapies.[9]

- For products that receive accelerated approval, we recommend that the post-approval study to verify the product's predicted effect on clinical benefit use ABR as the primary endpoint.

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 to reduce bleeding events in the prior 6 to 12 months. This baseline dose stability can facilitate efficacy assessments following administration of the GT product.
   - Observing subjects for 6 months (lead-in period) in-study to collect ABR data. ABRs based on retrospective data collection from medical records may be subject to recall bias and missing information. Collecting:

[8] The normal ranges of factor assays in each laboratory depend on the local population, sample preparation, assay methodology and a variety of additional circumstances

[9] Guidelines to determine the severity of hemophilia and correlation of severity of bleeding to factor activity are available. However, at present, evidence based guidelines with recommendations for a minimum target level of steady-state therapeutic factor activity for patients with severe hemophilia and pre-existing joint damage are unavailable.

  - 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:

- Including a plan for exogenous factor replacement therapy based on most recent factor activity levels for the management of interventional procedures and bleeding episodes.
- 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 should 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. 18) 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 BLA 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.

- As hemophilia affects both children and adults, pediatric studies are a critical part of drug development. 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.
- Plans to enroll pediatric subjects should be discussed with the Agency in the context of the anticipated benefit-risk profile of the product. Benefit-risk calculations for GT trials in pediatric patients with hemophilia should consider durability of expression, potential insertional mutagenesis, episomal dilution during liver growth, and the effect of transgene expression. To justify enrolling pediatric subjects, you should:
    - Submit clinical data from studies in adults to demonstrate sustained and robust steady state factor levels and hemostatic outcomes.
    - Select an appropriate pediatric population that represents a population with an unmet medical need in the context of available therapies.
    - Consider conducting studies in appropriate animal models to support sustained factor expression levels following GT product administration.
    - Consider characterizing the risks of your GT product (e.g., vector integration, insertional mutagenesis) based on available preclinical and clinical data for your product.

- Plans to address inclusion of clinically relevant populations with regard to age, race, and ethnicity should be discussed with the Agency.

D. Statistical Considerations

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

- We recommend that you develop an NI margin (*M*) for comparing ABR of the investigational GT product to that of current prophylaxis therapies in the within-subject comparison trial.

- The hypothesis test and confidence interval should accommodate the paired nature of the ABRs before and after GT for the same subject.

- Descriptive statistics, including graphical displays such as histograms and scatter plots of ABRs, can add valuable information to understand the treatment effect, and, therefore, should also be considered.

The within-subject comparison design provides an added advantage in evaluating the treatment effect of the investigational product by controlling for factors that may also influence the bleeding outcomes. Additional information on general statistical and clinical considerations for non-inferiority trials is described in FDA guidance (Ref. 19).

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 assays for the detection of anti-vector and anti-factor T cell reactivity (more frequent monitoring may be appropriate if immune-mediated hepatic dysfunction is suspected).

- 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. 20).

2. Long-Term Monitoring (≥2 years following GT product administration): Please refer to the FDA guidance on *Long Term Follow-Up After Administration of Human Gene Therapy Products* for recommendations on duration and design of long-term follow up (Ref. 14). Please be aware that, as additional relevant scientific data becomes available, FDA may revise its recommendations for duration of follow-up for adverse events.

We recommend:

- Monitoring for adverse events should consider: 1) several product characteristics (e.g., integrating vector, nonintegrating vector, genome editing) that may be specific to the product under study and 2) the findings from preclinical studies (Ref. 14).

- 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.

- Clinical evaluations and imaging to assess the impact of steady state factor activity levels on long-term functional and structural outcomes of hemophilic arthropathy.

F. Patient Experience

Patient experience data[10] 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 a BLA.

The treatment landscape for hemophilia is evolving. As is the case for other products we review, we intend to evaluate the benefit-risk profile of the investigational product in the context of the treatment landscape at the time of our review of a marketing application.

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. 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. 17 and 21).

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 prior to submission of the IND (Ref. 22), 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.[11]

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[10] 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/development-approval-process-drugs/cder-patient-focused-drug-development.

[11] 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.

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