FDA’s Human Gene Therapy Draft Guidances:
Steps Toward a Modern Framework for the Regulation of Gene Therapy

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On July 11, 2018, the U.S. Food and Drug Administration (FDA or the Agency) made available a suite of six scientific draft guidance documents on human gene therapy (GT) products. GT products are products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences.1 According to FDA Commissioner Scott Gottlieb, M.D., the draft guidances are “intended to serve as the building blocks of a modern, comprehensive framework for how [FDA will] help advance the field of gene therapy while making sure new products meet the FDA’s gold standard for safety and effectiveness.”2

The draft guidances cover a range of regulatory issues and follow FDA approval of several gene therapies in 2017.3 Three of the draft guidances update prior FDA guidance4 on GT product manufacturing, quality, and safety (collectively, the Manufacturing and Safety Draft Guidances):

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (CMC Draft Guidance)
- Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus (RCR) during Product Manufacture and Patient Follow-up (RCR Draft Guidance)

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3 BLA 125646/0, Approval Letter for Tisagenlecleucel (Aug. 30, 2017); BLA 125643/0, Approval Letter for Axicabtagene Ciloleucel (Oct. 18, 2017); BLA 125610/0, Approval Letter for voretigene neparvovec-rzyl (Dec. 19, 2017).
Long Term Follow-Up After Administration of Human Gene Therapy Products (LTFU Draft Guidance)

Also, for the first time, FDA issued draft guidances for disease-specific GT products (collectively, the Disease-Specific Draft Guidances):

- Human Gene Therapy for Rare Diseases (Rare Disease Draft Guidance)
- Human Gene Therapy for Hemophilia (Hemophilia Draft Guidance)
- Human Gene Therapy for Retinal Disorders (Retinal Disorders Draft Guidance)

Beyond the steps announced in the draft guidances, FDA intends to continue to work with GT product sponsors to make the development and approval of GT products more efficient. The Agency also will make “full use” of FDA’s expedited programs when possible, such as breakthrough therapy designation and regenerative medicine advanced therapy (RMAT) designation.

This alert summarizes key aspects of the draft guidances, beginning with the Manufacturing and Safety Draft Guidances and then turning to the Disease-Specific Draft Guidances. Stakeholders should consider submitting comments to the agency to help shape the direction of FDA’s final guidances on these topics. The FDA docket is open for comments until October 10, 2018.

I. Manufacturing and Safety Draft Guidances

In 2006 and 2008, FDA issued guidance documents on chemistry, manufacturing, and controls (CMC) of gene therapies; testing of retroviral vector-based gene therapies; and long-term follow-up (LTFU) studies for GT products. Since then, FDA has updated its thinking, given the rapid advances in technology. FDA’s current thinking is reflected in the new draft guidance documents (summarized below), which once finalized, will supersede their respective 2006 and 2008 counterpart guidances.

CMC Draft Guidance

The CMC Draft Guidance provides the sponsors of human gene therapy investigational new drug (IND) applications with recommendations for how to provide CMC information in an IND to assure FDA of the safety, identify, quality, purity, and strength of the investigational product. The draft guidance applies to GT products and combination products that contain a human gene therapy in combination with another drug or device.

The CMC Draft Guidance reflects FDA’s growing experience with GT products and aligns with the updated international standards on CMC, such as the International Conference on Harmonisation (ICH) Q12 draft guidance on post-approval changes. While the 2008 CMC Guidance instructed FDA reviewers how to review and assess CMC information as part of an IND review, the updated CMC Draft Guidance intends to serve as a roadmap to sponsors on how to incorporate CMC information within an IND submission. Accordingly, the draft guidance

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6 Id.
follows FDA’s Common Technical Document (CTD) structure as it details what CMC information sponsors should include within an IND.

Consistent with FDA’s CTD Guidance, FDA recommends that sponsors provide administrative information in Module 1. The module should contain administrative documents (e.g., application forms, cover letters, reviewer guides), and a copy of all labels and labeling provided to each investigator in the clinical study. Module 1 can also include, but is not required to include, information previously submitted to FDA. The sponsor may reference information previously submitted to FDA by another individual if the sponsor provides a Letter of Authorization granting the sponsor the right to cross-reference the previously submitted information.

Module 2 should contain a summary of quality information for the GT product, including a description of the product’s active ingredients, mode of action, and proposed clinical use. FDA has noted that firms often erroneously place the entire CMC section in Module 2 instead of providing the quality overall summary to summarize the CMC section in Module 3. Consistent with quality by design principles in ICH Q8, ICH Q11, and ICH Q12, among other ICH guidance documents, the sponsor should describe the critical quality attributes (CQAs) relevant to the safety and biological activity of the product. CQAs apply to the drug substance, the drug product, and excipients and in-process materials. Module 2 should differentiate between the drug substance and the drug product. For purposes of the CMC Draft Guidance, a drug substance is “an active ingredient that is intended to furnish biological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body.” A drug product is “the finished dosage form that contains the drug substance, generally, but not necessarily in association with one or more other ingredients (e.g., excipients).” FDA notes that “[s]ome gene therapy products may not have a defined DS whereas others “may consist of two or more different DSs that are combined to make the DP.” Due to the difficulty in distinguishing between drug substance and drug product in GT products, the draft guidance “does not recommend how sponsor should distinguish the DS and DP.” Instead, a sponsor can self-define but should explain how it distinguished the substance from the product.

Module 3 should contain detailed CMC information on the drug substance and the drug product. As with the 2008 CMC Guidance, a significant portion of the CMC Draft Guidance outlines how sponsors should submit detailed information on the manufacture, testing, and storage of the drug substance.

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8 CMC Draft Guidance, at 4.
9 See Bowman Cox, FDA’s CMC Guidance for Investigational Gene Therapies Reflects Broader CMC Evolution, Pink Sheet (July 11, 2018).
10 CQAs are “a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.” CMC Draft Guidance, at 5.
11 CMC Draft Guidance, at 5-6.
12 Id., at 6.
13 Id.
14 Id. FDA has noted outside of the CMC Draft Guidance that “viral vectors used for ex-vivo modification of cells” should be treated as drug substances. Cox, supra note 9.
The drug substance section of Module 3 should contain general information on the drug substance, details on manufacturing the drug substance, a characterization of the drug substance, testing and controls on the drug substance, reference materials used for testing, the containers and closures used for the drug substance, and stability testing and data. Manufacturing information should include (1) the name and address of each manufacturer, (2) a description of the manufacturing process, (3) a list of all materials used in manufacturing and a description of the quality and control of the materials, (4) control of critical steps and intermediates, (5) process validation studies, and (6) a description of the developmental history of the manufacturing process. FDA recommends using “FDA-approved or cleared or other clinical grade materials” for manufacturing, when such materials are available. When using cell banks to manufacture products, the CMC Draft Guidance urges sponsors to carefully consider and characterize the starting materials used to create each cell bank. In general, sponsors should describe the history of the cell bank source, how the bank was generated, and the genetic profile of the source.

Consistent with past guidance, FDA recommends that the IND application include specifications for drug substances. The CMC Draft Guidance elaborates in detail about the tests that manufacturers of GT products should conduct to ensure drug substance quality and safety. FDA advises that sponsors test for process-related impurities (e.g., residual nucleic acid), and conduct safety testing (e.g., microbiological testing) to ensure product quality. Documentation on analytical procedures should describe “how a procedure is performed and should specify any reference standards, equipment, and controls to be used.” FDA advises sponsors to develop “detailed” SOPs for how analytical procedures to assess product quality are conducted early in product development. To ensure safety, FDA recommends that sponsors qualify the assays to determine dose prior to initiating dose escalation studies. Quantitating preclinical and clinical lots can help ensure the comparability of doses used for preclinical and clinical evaluations.

FDA’s CMC recommendations on the drug product mirror the guidance provided in the drug substance section. A sponsor should describe the drug product, how the sponsor will manufacture the drug product, how the sponsor will control excipients, and how the sponsor will control the drug product (e.g., specifications and analytical procedures). The drug product section should also provide a description of reference materials, container closure systems, and stability testing and data. The section also should detail the drug development studies conducted to establish product formulation, manufacturing process, container closure system, microbiological attributes, and instructions for use.

Sponsors can provide additional CMC information in the appendices. FDA recommends that sponsors include a diagram of the manufacturing process and describe the facility and equipment used to make the drug substance and drug product. The appendices could also describe how sponsors tested for risk of contamination with adventitious agents (e.g., bacteria and fungi) unintentionally introduced into the manufacturing process.

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15 CMC Draft Guidance, at 12.
16 Id., at 17-24.
17 Id., at 30.
18 Id.
19 Id., at 36-48.
RCR Draft Guidance

The RCR Draft Guidance provides sponsors of retroviral vector-based GT products recommendations for testing for RCR during product manufacturing and follow-up monitoring of treated patients. Retroviral gene therapy research typically employs replication-defective retrovirus (i.e., retrovirus where the part of the viral genetic material required for replication is missing) so that the virus cannot replicate and disrupt the host genome. RCR, however, can develop any time during product manufacturing, for example, through homologous or non-homologous recombination between the transfer vector, packaging components, and endogenous retroviral elements in producer cells.20 Testing, therefore, should occur during multiple stages of the production and product-testing process. RCR test results should be documented in amendments to the IND file (negative results via the IND annual report, and positive results from patient monitoring via an IND safety report).21

Once finalized, the RCR Draft Guidance will replace a prior guidance on this topic that FDA issued in 2006 (the 2006 RCR Guidance). In the period between the two guidances, the gene therapy community has made important progress in reducing the likelihood of RCR and the amount of scientific and safety data available on retroviral vectors has increased significantly.22 In light of these developments, the RCR Draft Guidance updates FDA’s recommendations for RCR testing in several ways.

First, FDA is no longer recommending that sponsors conduct RCR testing on working cell banks (WCBs) for retroviral producer cells. A WCB is a cell bank derived from one or more ampules of a master cell bank (MCB)23 that is expanded by serial subculture to a specified passage number.24 Second, instead of testing based on product lot size, the RCR Draft Guidance recommends that sufficient supernatant be tested to demonstrate a 95% probability that the vector contains less than 1 RCR per patient dose.25 Third, the 2006 RCR Guidance recommended archiving ex vivo transduced cells that had been cultured for less than four days, rather than active testing.26 The RCR Draft Guidance, however now recommends that these products also be tested for RCR such that “each lot of ex vivo transduced cells and culture supernatant be tested for RCR.”27 If, however, a sponsor has manufacturing and clinical

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22 Id., at 2-3.

23 A master cell bank is “a collection of cells of uniform composition derived from a single tissue or cell.” 2006 RCR Guidance, at 2.

24 Id.; see also RCR Draft Guidance, at 4; CBER, FDA, Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (July 12, 1993), at 9, https://www.fda.gov/downloads/biologicsbloodvaccines/safetyavailability/ucm162863.pdf.


26 2006 RCR Guidance, at 8.

27 RCR Draft Guidance, at 5.
experience data that demonstrate a consistently RCR-negative product, this testing may be reduced or eliminated.28

Consistent with past recommendations, the RCR Draft Guidance recommends that both cells and supernatant from the vector producer cell (VPC) MCB be tested for RCR on a cell line permissive for infection by the relevant RCR.29 End-of-production cells—i.e., cells from which is taken (a) a single bulk harvest of retrovirus-containing supernatant, or (b) the last of a serial set of supernatant harvests—should also be tested for RCR.30 FDA recommends that sponsors test 1% or 10⁸ (whichever is less) pooled vector-producing cells or ex vivo transduced cells by co-culture.31 For both vector supernatant testing and cell testing, culture and co-culture assays (respectively) should be developed with a permissive cell line for a minimum of five passages to amplify any potential RCR present.32 Alternative methods may be appropriate, but should be developed in consultation with the Center for Biologics Evaluation and Research (CBER).33 It is recommended that sponsors develop an in-house reference standard that represents the sponsor’s clinical vector attributes (e.g., genetic background, envelope protein, deletion of accessory proteins) for use as a positive control and for method validation.34

FDA has revised its recommendations for patient-monitoring RCR testing to be more responsive to accumulated data for each GT product. Prior guidance recommended RCR testing and/or archiving of patient samples at specified intervals for fifteen years.35 The RCR Draft Guidance states, however, that if all post-treatment assays are negative during the first year, collection of yearly follow-up samples may be discontinued.36 FDA’s revised recommendations are informed by the fact that, “[t]o date, RCR or delayed adverse events related to RCR have not been reported in patients who have received retrovirus-based gene therapies.”37 The Agency continues to recommend that annual clinical history be obtained to determine clinical outcomes suggestive of retroviral disease (e.g., cancer, neurologic disorders, hematologic disorders).38 If an adverse event suggestive of retroviral disease occurs, samples should be collected and tested for RCR.39 To test for RCR, FDA recommends that sponsors use either serologic

28 Id.
29 Id.; 2006 RCR Guidance, at 2-3. If the VPC is derived at any step with an ecotropic retroviral vector, the MCB should be tested for the ecotropic RCR. RCR Draft Guidance, at 4.
30 RCR Draft Guidance, at 5.
31 Id., at 7.
32 Id.
33 Id., at 7-8.
34 Id., at 8.
35 2006 RCR Guidance, at 7-8; 2006 Delayed Adverse Events Guidance, at 3.
36 RCR Draft Guidance, at 8. The RCR Draft Guidance otherwise recommends the same testing schedule as previously recommended in the 2006 RCR Guidance: patient samples be analyzed at pre-treatment, followed by testing at three, six, and twelve months after treatment, and yearly for up to fifteen years. Id.
37 Id.
38 Id., at 9.
detection of RCR-specific antibodies or a polymerase chain reaction assay for RCR-specific DNA sequences.40

The RCR Draft Guidance includes new post-licensure and other recommendations. FDA recommends that labeling for retroviral vector-based GT products clearly presents the immediate and long-term risks associated with RCR.41 In addition, a sponsor’s biologics license application (BLA) for a retroviral GT product should include sufficient manufacturing and clinical safety data to determine the product’s RCR risk.42 If this risk assessment is used to propose that periodic patient monitoring is not warranted, sponsors should still include a provision in the marketing application to collect clinical samples from patients for RCR testing upon development of an adverse event suggestive of a retrovirus-associated disease.43 As discussed below, patients should be followed for up to fifteen years following product licensure to monitor for delayed adverse events.44

**LTFU Draft Guidance**

The LTFU Draft Guidance updates FDA’s recommendations on the design of long-term observational studies for the collection of data on delayed adverse events following use of a GT product. In its 2006 Delayed Adverse Events Guidance, the Agency advised sponsors to observe subjects for delayed adverse events for up to fifteen years following exposure to an investigational GT product, including at least five years of annual examinations followed by ten years of annual queries (either in-person or by questionnaire). Clinical experience gained since 2006 and the emergence of novel GT products and technologies (e.g., gene editing) led FDA to update its recommendations.

The LTFU Draft Guidance notes that not all GT products will require long-term follow-up (LTFU) observational studies,45 and suggests the following framework to help GT-product sponsors assess the risk of delayed adverse reactions and thus the need for LTFU observations.

40 Id.
41 Id., at 10.
42 Id.
43 Id.
44 Id.
45 LTFU Draft Guidance, at 1.
FDA explains that it “consider[s] the assessment of risk to be a continuous process” and sponsors should reassess the need for LTFU observations or the design of long-term observational studies as more data accumulate.\textsuperscript{46} In addition to product-related factors and preclinical information about the product (e.g., biodistribution studies, vector persistence and integration studies) a sponsor should consider the target cell/tissue/organ, the patient population (e.g., age, immune status, risk of mortality), and relevant disease characteristics to assess the GT product’s long-term risk profile.\textsuperscript{47} Data from a similar product also may be relevant to assessing the need for LTFU observations.\textsuperscript{48} If a sponsor has evidence that its GT product is unlikely to persist in human hosts, or the vector sequence does not integrate into the human genome and the product does not have latency or reactivation potential, a sponsor could submit a clinical protocol that does not provide for LTFU observations. Of course, if FDA disagrees it may place the study on clinical hold.\textsuperscript{49}

An LTFU observational study is intended to identify and mitigate the long term risks to patients receiving a GT product. All study subjects who receive the product should be enrolled in the LTFU study (after providing informed consent).\textsuperscript{50} In general, FDA recommends that LTFU protocols have a duration of fifteen years for integrating vector products, up to fifteen years for genome-editing products, and up to five years for adeno-associated virus vector products.\textsuperscript{51} Sponsors should develop clinical protocols that detail patient visit schedules, sampling plans,

\textsuperscript{46} Id., at 5.

\textsuperscript{47} Id., at 3. For products that involve gene editing, FDA recommends that sponsors consider the cell type that is modified \textit{ex vivo} and the vector used to deliver the genome-editing component, among other things, as part of the product’s preclinical safety evaluation to inform the scope of LTFU studies. Id., at 15.

\textsuperscript{48} Id., at 5.

\textsuperscript{49} Id., at 8-9.

\textsuperscript{50} Id., at 16.

\textsuperscript{51} Id.
test-monitoring methods, and clinical events of interest. Annual physical examinations should be performed by health care providers during the first five years (or until completion of the study if less than five years) unless the product’s risk assessment indicates more frequent examinations are needed. Study subjects should be tested at least annually for persistent vector sequences until they become undetectable. The LTFU Draft Guidance also sets forth data collection recommendations, IND safety reporting and annual reporting requirements, and informed consent considerations for LTFU studies, as well as recommendations specific to integrating-vector GT products and genome-editing products.

Given that LTFU studies are often necessary after licensure of the GT product, FDA recommends that a sponsor submit a Pharmacovigilance Plan at the time of the BLA submission for the product. The Agency may recommend specific pharmacovigilance measures, such as establishing a registry for sample collections or following adverse events to resolution. The Agency will also determine whether a Risk Evaluation and Mitigation Strategy is necessary for a GT product. FDA recommends that a sponsor consult with the Office of Tissues and Advanced Therapies on the plans for completing an LTFU study if the sponsor decides to inactivate, transfer, or withdraw an IND, or cease to operate.

II. Disease-Specific Draft Guidances

FDA’s Disease-Specific Draft Guidances address CMC, preclinical development, and clinical trial considerations of particular relevance to rare diseases, hemophilia, and retinal disorders. All three draft guidances recommend that the preclinical program for the GT product address five overall objectives:

- identification of a biologically active dose range;
- recommendations for an initial clinical dose level, dose-escalation schedule, and dosing regimen;
- establishment of feasibility and reasonable safety of the proposed clinical route of administration (ROA);
- support of patient eligibility criteria; and


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52 Id., at 17.
53 Id., at 20-21.
54 Id., at 19-26.
55 Id., at 26.
56 Id., at 27.
57 Id.
58 Id.
identification of potential toxicities and physiologic parameters that help guide clinical monitoring for a particular investigational product.\(^6^0\)

FDA recommends that preclinical programs for investigational GT products include \textit{in vitro} and \textit{in vivo} proof-of-concept (POC) studies, biodistribution studies, toxicology studies that incorporate the elements of the planned clinical trial, and, as applicable for GT products for rare diseases and hemophilia, additional nonclinical studies to address (1) the possibility of developmental and reproductive toxicity, and (2) significant manufacturing or formulation changes that may impact the comparability of the clinical trial GT product and the GT product intended for licensure.\(^6^1\)

The Disease-Specific Draft Guidances all recommend that sponsors collect patient experience data and submit such data with the marketing application.\(^6^2\) The draft guidances also highlight the availability of potentially applicable expedited programs (particularly RMAT designation) and the importance of early communication with the Office of Tissues and Advanced Therapies (OTAT) through pre-IND meetings or INTERACT meetings (formerly pre-pre-IND meetings).\(^6^3\)

**Rare Diseases Draft Guidance**

Because of the challenges inherent in developing GT products for rare diseases, FDA emphasizes the importance of addressing CMC issues early in the development process.\(^6^4\) Traditionally, sponsors evaluate CQA in each phase of development and correlate characterization data from many product lots to clinical outcomes. But the limited population size and diverse variations or sub-types of many rare diseases complicates product development because small study populations might lead to fewer manufacturing runs and fewer lots. This can complicate the establishment of critical process parameters (CPP) to ensure product CQA.\(^6^5\) To overcome this challenge, sponsors developing GT products for rare diseases can consider "innovative strategies" for characterizing product CQA and implementing manufacturing CPP early in clinical development, such as by using multiple small lots rather than a single large lot.\(^6^6\) FDA strongly encourages sponsors to contact OTAT prior to IND submission to discuss product-specific considerations such as the effect of product-related

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\(^6^0\) Rare Diseases Draft Guidance, at 3; Hemophilia Draft Guidance, at 4; Retinal Disorders Draft Guidance, at 2-3.

\(^6^1\) Rare Diseases Draft Guidance, at 4; Hemophilia Draft Guidance, at 5; Retinal Disorders Draft Guidance, at 3.

\(^6^2\) As defined in section 569(c) of the Federal Food, Drug, and Cosmetic 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." Rare Diseases Draft Guidance, at 10 n.5.

\(^6^3\) See also INTERACT Meetings (INitial Targeted Engagement for Regulatory Advice on CBER producTs), https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/umd611501.htm (last accessed July 13, 2018).

\(^6^4\) Rare Diseases Draft Guidance, at 2.

\(^6^5\) Id.

\(^6^6\) Id.
variations on interpretability of smaller rare disease studies; establishing a potency test and qualifying it for suitability prior to conducting trials; and issues related to process manufacturing development, comparability studies, and process validation.67

With respect to the preclinical program of a GT product for a rare disease, FDA notes that most rare diseases are pediatric diseases or have pediatric onset.68 Accordingly, in addition to the preclinical program objectives and studies outlined above, the preclinical program for a rare disease GT product may also need to demonstrate a prospect of direct benefit in order to justify conducting first-in-human clinical trials in pediatric subjects.69

Many general considerations for GT clinical trials are addressed in other FDA guidance,70 but rare diseases present additional complications because of limited population size, phenotypic heterogeneity, insufficient information about the natural history of the disease, and issues related to conducting clinical trials in pediatric populations.71 Therefore, the Rare Diseases Draft Guidance recommends that sponsors of GT products for rare diseases consider the following elements during clinical development:

- **Study Population.** For diseases caused by a genetic defect, sponsors should perform genetic tests for the defect in all clinical trial subjects. Sponsors may choose to exclude patients with pre-existing antibodies to the GT product, and if so, should strongly consider developing a companion diagnostic. Severity of the disease and involvement of pediatric patients in clinical trials are also important considerations. Healthy volunteers generally should not be enrolled in GT studies, and a well-written informed consent document is essential.72

- **Study Design.** Due to the limited number of patients typically available for rare disease studies, as much pertinent data as possible should be collected from every subject. The randomized, concurrent-controlled trial is generally considered the ideal standard for establishing effectiveness. The draft guidance also recommends that sponsors consider, among other things:
  - designing the first-in-human study to be an adequate and well-controlled investigation with the potential to provide evidence of effectiveness;

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67 Id., at 2-3.

68 Id., at 6.

69 Id., at 3-4. See also 21 C.F.R. § 50.53 (describing additional safeguards for children in clinical investigations).

70 Supra, note 60.

71 See Rare Diseases Draft Guidance, at 5.

72 See LTFU Draft Guidance, at 21-22 and 24-25, for guidance on informed consent in trials involving long term follow-up observations, including special considerations for trials involving retroviral vectors. See also Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products: Guidance for Industry (June 2015), at 21 (recommending that when there is a separate protocol for long-term monitoring, subjects should be consented for all long-term monitoring before participating in the initial GT trial), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf, at 21.
• promoting data interpretability by using stratified randomization based on disease stage/severity;
• using an intra-subject control design for certain GT indications;
• using a single-arm trial with historical controls, if there are feasibility issues with conducting randomized, controlled trial (knowledge of the natural history of the disease will be critical)

- **Dose Selection.** Dose selection should be informed by all available sources of clinical information and should leverage non-human data. Early-phase studies should include two or more dose levels (ideally with placebo controls). Repeated dosing may not be an acceptable risk until toxicity and duration of activity are understood. Biomarkers should be identified and validated early in the process. When very closely linked to the underlying pathophysiology of the disease, changes in such biomarkers could be used for dose selection or even early demonstration of drug activity.

- **Safety Considerations.** Clinical trials should include an adequate monitoring plan. Product-directed immune responses may be an important consideration. Administration of the GT product should be staggered in most first-in-human trials, and sponsors should discuss the dosing interval and cohorts with OTAT in advance. Sponsors should also consider issues with long-term follow-up, study-stopping rules, and the potential for viral shedding.

- **Efficacy Endpoints.** Endpoint selection should consider: pathophysiology and natural history (particularly to identify potential surrogate endpoints for accelerated approval), specific aspects of the disease that are meaningful to the patient and might also be affected by the GT product’s activity, and longitudinal profiling.

- **Patient Experience.** Sponsors should collect and submit patient experience data.

**Hemophilia Draft Guidance**

The Hemophilia Draft Guidance primarily addresses considerations for factor activity measurements, preclinical studies, and clinical trials of GT products intended to treat hemophilia.73 One-stage clotting (OC) and chromogenic (CS) assays for measuring factor activity have been observed to produce different results across hemophilia products.74 Discrepancies have also been observed between types of OC reagents.75 These discrepancies pose challenges for using factor activity as a surrogate endpoint for hemostatic efficiency because the assay results for subjects treated with GT products cannot be reliably compared against previous experience with other hemophilia products.76 Addressing discrepancies between factor activity assays is also important for safe management of patients in GT clinical trials.77 For example, such assays are used to guide exogenous replacement therapy, as well as during follow-up monitoring of the safety and durability of response after GT product

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73 General CMC considerations for hemophilia GT products are the same as for other GT products. Hemophilia Draft Guidance, at 2.
74 Id., at 3.
75 Id.
76 See id.
77 Id.
administration. The Hemophilia Draft Guidance provides recommendations for sponsors to better interpret factor activity measurements from OC and CS clinical laboratory assays and recommends that sponsors clarify the biochemical root-causes for any discrepancies observed.

Data from preclinical studies should inform which assays a sponsor selects for early-phase clinical studies. Sponsors should consider performing a comparative field study with patient plasma samples and bridging studies if the assay(s) are changed during the study. In addition to the preclinical program elements described above, sponsors of GT products for hemophilia should include use of an identical assay for vector titer determination in preclinical and clinical lots.

For clinical development programs, the draft guidance’s recommendations include:

- **Efficacy Endpoints.** Sponsors should use the Annualized Bleeding Rate (ABR) as a primary endpoint to demonstrate clinical benefit for traditional approval, and factor activity as a surrogate endpoint for primary efficacy for accelerated approval (subject to certain conditions).

- **Study Design.** Sponsors should consider, among other things, including a six-month lead-in period to observe patients and collect data for ABR rates and enrolling patients who use on-demand therapy prior to study entry in a separate cohort. Post-administration, sponsors should use the same exogenous replacement therapy as used in the lead-in phase. FDA also recommends: 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 exogenous factor prophylaxis; specifying when assessment of ABR rates and durability of response is to begin; collecting data for analyses of supportive endpoints; including a plan for management of immune-mediated liver dysfunction; and including an assessment plan to correlate factor activity and bleeding rates.

- **Study Population.** Sponsors may choose to exclude patients with pre-existing antibodies to the GT product, and if so, should strongly consider developing a companion diagnostic. Special considerations for the involvement of pediatric patients in clinical trials are likely to be relevant, and adequate steps must be taken to obtain permission of responsible adult(s) and assent of the child.

- **Statistical Considerations.** For traditional approval, FDA recommends a non-inferiority clinical trial design with ABR as the primary efficacy endpoint using a within-subject comparison design.

- **Short- and Long-term Study Monitoring.** The overall goal is to monitor the safety and durability of response. “Short-term” is the first two years following GT product administration, and “long-term” is the period greater than or equal to two years following administration.

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78 See id., at 3-4, 7-8, and 9.
79 Id., at 3.
80 Id.
81 Id., at 4-5.
82 Id., at 8. See 21 C.F.R. §§ 50.52, 50.53, 50.55.
GT product administration. Long-term monitoring recommendations include monitoring for adverse events for at least five years after exposure to non-integrating GT products and 15 years for integrating GT products, monitoring for inhibitor antibodies to factor VIII or factor IX, monitoring for the emergence of new clinical conditions, and monitoring factor activity at least once every six months for five years.

- **Patient Experience Data.** Sponsors should collect and submit patient experience data.

**Retinal Disorders Draft Guidance**

The Retinal Disorders Draft Guidance addresses considerations for product development, preclinical studies, and clinical trials for GT products for adult and pediatric retinal disorders.

In addition to the general CMC considerations applicable to GT products, certain other CMC considerations apply to retinal disorder GT products. These include: consideration of the final product formulation and concentration to meet the expected dose and volume requirement; an endotoxin limit for intraocular delivery (USP <771>); product testing of GT vector-based final products for particulate matter in accordance with USP <789>; testing of the final product configuration in product testing and release; and evaluating compatibility of the GT product and delivery system.83

In addition to the preclinical study considerations described above, sponsors of investigational GT products for retinal disorders should use animal species and/or models in POC studies that demonstrate a biological response to the product that is similar to the expected response in humans.84 Although rat and mouse animal models of retinal disorders are often used in POC studies, the draft guidance notes that inclusion of larger animals with more “human-like” eyes may provide applicable safety information and facilitate experience with the intended surgical procedures and delivery systems.85 The draft guidance highlights the importance of differences between the immune responses of animals and humans, and explains that “clinical data, rather than preclinical data, may provide the most relevant safety information for repeat product administration.”86 For toxicity studies, “sponsors should determine the frequency, severity, potential cause, and clinical significance” of any abnormal ophthalmic findings or lesions, and should also further characterize inflammatory or immune responses to assess potential attribution to the vector or transgene.87

For clinical development programs, the Retinal Disorders Draft Guidance’s recommendations include:

- **Natural History Studies.** Sponsors should perform a careful natural history study if existing data are insufficient, as is often the case for rare degenerative retinal disorders. FDA welcomes early interaction on these study designs.

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83 Retinal Disorders Draft Guidance, at 2.
84 Id., at 3.
85 Id., at 3-4.
86 Id., at 4.
87 Id., at 3.
Life Sciences

- **Study Design.** The draft guidance provides several recommendations regarding controls and reduction of potential bias.
  - A randomized, concurrent parallel control group should be used whenever possible. Administration of the vehicle alone may serve as a control, but intravitreal or subretinal injection of the vehicle alone may not be ethically acceptable under certain circumstances. FDA recommends other options such as alternative dosing regimens, alternative dose levels, and use of products approved for the indication being sought.
  - Concurrent parallel groups and adequately-designed masking procedures should be used to reduce potential bias, as patient effort can influence measurements of endpoints such as visual acuity. A least two treatment arms with different doses should be used, in addition to a sham control group, because patients may be able to identify differences between the product delivery procedure and sham procedure.
  - Use of the contralateral eye as a control is generally not recommended because (1) the eyes are often at different stages of disease and progression is not necessarily similar, and (2) exposing a patient to both the GT and sham procedures frequently leads to unmasking.
- **Study Population.** A companion diagnostic should be developed, if needed, to confirm the genetic mutation. In general, first-in-human GT trials should enroll patients with severities of visual impairment that offer a favorable risk-benefit profile. As with other products used to treat pediatric patients, additional considerations apply.\(^{88}\)
- **Study Use.** Recommendations include: dose-ranging designs for early-phase trials; consideration of administration in both eyes (e.g., sequentially, selecting which eye to receive the product first, determining the time interval); ensuring consistency in the product delivery procedure across study sites; and studies to explore the feasibility of repeat administration in the same eye.
- **Safety Considerations.** Intraocular administration should be performed by experienced individuals. Because local or systemic immune responses may pose important safety risks, immunosuppressant drugs may be considered and patients should be closely monitored and treated as necessary to minimize the risk of complications.
- **Study Endpoints.** Sponsors should “explore a wide spectrum of potential clinical endpoints and other clinical effects in early-phase trials.”\(^{89}\) Primary endpoints in later phase trials should reflect clinical benefit (e.g., improvement in function or symptoms). Established efficacy endpoints include best corrected distance visual acuity and rate of photoreceptor loss, but novel efficacy endpoints are encouraged, particularly for rare retinal disorders where established endpoints may not be appropriate.
- **Follow-Up Duration.** Duration will be product-specific. Sponsors should evaluate durability of the clinical effect and should refer to the LTFU Draft Guidance for more detailed discussion.
- **Patient Experience.** Sponsors should collect and submit patient experience data.

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\(^{88}\) See 21 C.F.R. §§ 50.52, 50.53, 50.55.

\(^{89}\) Retinal Disorders Draft Guidance, at 8.
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