

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products

Guidance for Industry

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Table of Contents

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	FEATURES OF CGT PRODUCTS THAT INFLUENCE CLINICAL TRIAL DESIGN	3
	A. Product Characteristics.....	3
	B. Manufacturing Considerations.....	5
	C. Preclinical Considerations.....	5
IV.	CLINICAL TRIAL DESIGN	6
	A. Early-Phase Trial Objectives	6
	B. Choosing a Study Population.....	8
	C. Control Group and Blinding.....	12
	D. Dose and Regimen.....	14
	E. Treatment Plan.....	15
	F. Monitoring and Follow-up	18
V.	MEETINGS WITH OCTGT	22
VI.	GUIDANCE ON SUBMITTING AN IND.....	22
VII.	REFERENCES.....	24

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I. INTRODUCTION

The Center for Biologics Evaluation and Research (CBER)/Office of Cellular, Tissue, and Gene Therapies (OCTGT) is issuing this guidance to assist sponsors and investigators in designing early-phase clinical trials for cellular therapy (CT) and gene therapy (GT) products. CT and GT products will be referred to collectively as CGT products. This guidance provides OCTGT's current recommendations regarding clinical trials in which the primary objectives are the initial assessments of safety, tolerability, or feasibility of administration of investigational products. Such trials include most Phase 1 trials, including the initial introduction of an investigational new drug into humans, and some Phase 2 trials of CGT products.

The scope of this guidance is limited to products for which OCTGT has regulatory authority. CGT products within the scope of this guidance meet the definition of "biological product" in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) and include CT and GT products that are used as therapeutic vaccines.¹ This guidance does not apply to those human cells, tissues, and cellular- and tissue-based products (HCT/Ps) regulated solely under section 361 of the PHS Act (42 U.S.C. 264), as described in Title 21 of the Code of Federal Regulations (CFR) Part 1271 (21 CFR Part 1271), or to products regulated as medical devices under the Federal Food, Drug, and Cosmetic Act, or to therapeutic biological products for which the Center for Drug Evaluation and Research (CDER) has regulatory responsibility.

There is increasing interest and activity in the development of CGT products because of their potential to address unmet medical needs. This guidance is intended to facilitate such development by providing recommendations regarding selected aspects of the design of early-phase clinical trials of these products. This guidance does not provide detailed information about the preclinical and chemistry, manufacturing, and controls (CMC) components of an

¹ Many of the principles in this guidance may apply to combination products involving a biological product under OCTGT's regulatory authority.

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investigational new drug application (IND), as we have previously provided recommendations in connection with these components (Refs. 1, 2, and 3). This guidance is intended to complement the information in those guidances.

This guidance finalizes the draft guidance of the same title dated July 2013.

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.

II. BACKGROUND

The design of early-phase clinical trials of CGT products often differs from the design of clinical trials for other types of pharmaceutical products. Differences in trial design are necessitated by the distinctive features of these products, and also may reflect previous clinical experience.

Early experiences with CGT products indicate that some CGT products may pose substantial risks to subjects. These experiences include multi-organ failure and death of a subject who received a GT product for ornithine transcarbamylase deficiency (Ref. 4), late-onset T-cell leukemia in subjects who received a GT product for X-linked severe combined immunodeficiency (X-SCID) (Ref. 5), and development of tumors in the brain and spinal cord of a patient who received intrathecal allogeneic stem cells for ataxia telangiectasia (Ref. 6). These events illustrate that the nature of the risks of CGT products can be different from those typically associated with other types of pharmaceuticals.

Features of some CGT products that may contribute to their risks include the potential for prolonged biological activity after a single administration, a high potential for immunogenicity, or the need for relatively invasive procedures to administer the product. Unlike many small molecule pharmaceuticals, the logistics and feasibility of manufacturing a CGT product sometimes influence the design of the clinical trials. In addition, the preclinical data generated for CGT products may not always be as informative as for small molecule pharmaceuticals, particularly since it usually is not feasible to conduct traditional preclinical pharmacokinetic (PK) studies with CGT products.

Thus, the design of early-phase clinical trials of CGT products often involves consideration of clinical safety issues, preclinical issues, and CMC issues that are encountered less commonly or not at all in the development of other pharmaceuticals. Section III of this guidance describes some distinctive features of CGT products and their development. Section IV discusses specific aspects of the design of early-phase trials of CGT products, based on consideration of the issues presented in Section III. Therefore, Section IV focuses on elements of trial design that may be different for CGT products than for other types of pharmaceuticals. Finally, Sections V and VI offer brief recommendations regarding IND submissions and meetings with OCTGT.

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III. FEATURES OF CGT PRODUCTS THAT INFLUENCE CLINICAL TRIAL DESIGN

The design of early-phase clinical trials of CGT products is influenced by their many distinctive features. These features include product characteristics and manufacturing considerations, some of which are unique to CGT products, and can dictate critical elements of the clinical trial design. In addition, the preclinical studies conducted in support of the clinical trial design are often different from those for other types of products. This section describes some of these special features. Section IV describes how these special features influence the design of clinical trials for CGT products.

A. Product Characteristics

1. Characteristics of Both CT and GT Products

In contrast with some well-studied classes of small molecules, there is a relative lack of clinical experience with some CGT products. In the absence of substantial experience across a broad population, there can be considerable uncertainty about the nature and frequency of safety problems that might be associated with specific types of CGT products.

Also, some CGT products can persist in humans for an extended period after administration, or have an extended or permanent effect even after the product itself is no longer present. The effects of the product might evolve over time (e.g., stem cells that proliferate and differentiate). Therefore, evaluation of safety and pharmacologic activity might require observation of subjects for a substantial period of time to understand the safety profile. Additional information about duration of follow-up can be found in Section IV.F.3 of this guidance.

CGT products may require surgery or other invasive procedures for delivery to the target site. The risks added by the use of an invasive procedure might be a substantial component of the overall risk of treatment, particularly when the product is administered into a relatively sensitive site, such as the heart or central nervous system. In some cases, product delivery may require use of an investigational device. The use of an existing, legally marketed device for administering a CGT product also may be investigational. As indicated in Section V of this guidance, it is appropriate to discuss clinical issues related to such usage in the pre-IND meeting. Furthermore, when surgery or other invasive procedures are required, the training of those responsible for administering the product might affect the safety and reliability of the administration procedure (see Section IV.E.3).

Allogeneic CT products, GT vectors, and proteins that might be produced by CGT products have the potential to elicit immune responses (immunogenicity). The induction of an immune response may be the desired effect of some products, such as therapeutic vaccines. For other CGT products, immunogenicity may be a risk. For

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example, pre-existing antibodies, or antibodies that develop after administration of the product, could reduce or extinguish a beneficial effect, cause an adverse reaction (e.g., an autoimmune syndrome), or influence safety or efficacy if there are any subsequent administrations. Also, in patients who have a condition that could be treated with a cellular, tissue, or organ transplant in the future, the development of antibodies to an allogeneic CGT product might jeopardize the success of the future transplant.

2. Characteristics of CT Products

CT products have unique complexities due to the dynamic nature of living cells. For example, cells may present a variety of molecules on their membranes and express a variety of factors. These molecules and factors may be affected by the microenvironment and change over time. Cells may differentiate *in vivo* into undesired cell types. Cells might also develop undesired autonomous functions, such as cells with the characteristics of cardiomyocytes forming a focus that generates electrical activity uncoordinated with the rest of the heart (Ref. 7). Stem cells, which have the potential to develop into a variety of mature tissue types, may undergo transformation and begin forming tumors (Ref. 6). In addition, a CGT product may include a variety of cell types, and it may be unclear which cell type or types are responsible for any specific toxic or therapeutic effect.

Another distinctive feature of cells is the ability to migrate. Systemic delivery of CT products may result in cells being distributed to a variety of tissues in the body; even cells delivered to a specific tissue or organ may migrate to unintended locations (Ref. 8).

The source (donor) of the cells or tissue may be the subject to be treated (autologous), or another individual (allogeneic). In some cases, the donor may receive a treatment prior to the harvest of source material. If the donor is also the trial subject, such pre-treatment may add to the overall risk to the subject.

Similarly, some CT products require pre-treatment of the recipient, e.g., with immune modification or myeloablative conditioning to facilitate cell survival. In such cases, the risks associated with the pre-treatment should be considered in the overall benefit-risk assessment.

3. Characteristics of GT Products

Several characteristics of GT products can influence trial design. For example, expression of a delivered gene may be uncontrolled and interfere with normal function of a critical enzyme, hormone, or biological process in the recipient. Some GT products are designed to integrate into the DNA of the recipient's cells to allow for long-term expression of the integrated genes. This genomic alteration could cause activation or inactivation of neighboring genes and give rise to benign or malignant

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tumors (Ref. 5). In addition, GT products with a viral or bacterial vector present the possibility of shedding, i.e., excretion/secretion of viral particles or bacteria that could be transmitted to other individuals.

4. Characteristics of Gene-Modified Cellular Products

Gene-modified cells, or ex vivo GT products, are products in which a gene is introduced into cells ex vivo, and then the modified cells are administered to the subjects. Products of this type have features, and potential risks, of both GT and CT products. Therefore, clinical trial design considerations of both GT and CT products apply to gene-modified cells.

B. Manufacturing Considerations

The scientific or logistical complexities of manufacturing CGT products may impose practical limits on the dose of the product that can be produced, or may limit the concentration or volume of product that can be delivered. These factors might therefore restrict the range of doses that are feasible in an early-phase trial. The implications of these factors for trial design are discussed in Sections IV.A.1 and IV.D.

For autologous products or patient-specific allogeneic donor products, unique product lots are manufactured for each subject, and potentially for each dose a subject receives. For such products, the inability to control factors such as subject-to-subject variability can contribute to product complexity. Some CGT products may take several weeks to months to produce. A failure or delay in manufacturing could prevent a subject from being treated as intended. For other patient-specific products, cell viability and potency may decline rapidly from the time of formulation. Therefore, “fresh” cells that are not cryopreserved may require administration within hours of manufacturing. Trial design considerations for patient-specific products are discussed in Section IV.E.4.

C. Preclinical Considerations

Preclinical in vitro and in vivo proof-of-concept, pharmacology, and toxicology studies are conducted to establish feasibility and rationale for clinical use of the investigational CGT product, as well as characterize the product’s safety profile. These studies also provide the scientific basis to support the conclusion that it is reasonably safe to conduct the proposed clinical investigations (21 CFR 312.23(a)(8)). Due to the diverse biology and scientific issues associated with CGT products, it is important to conduct a careful benefit-risk analysis, performed in the context of the particular clinical condition under study. Preclinical data generated from studies conducted in appropriate animal species and animal models of disease contribute to defining reasonable risk for the investigational CGT product.

Several issues can limit the ability of the preclinical data to guide various aspects of the design of the early-phase clinical trial. For example, the extrapolation of a potentially safe and possibly bioactive starting clinical dose from the animal data can depend on

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various factors, such as the animal models used, the clinical route of product administration, the biodistribution profile, and any immune response to the administered CGT product. However, traditional PK study designs are generally not feasible for CGT products; thus, such data are not available to guide clinical trial design. Due to various issues, such as species specificity and immunogenicity, extrapolation from a CGT product dose administered in animals to a clinical dose can be less reliable than the customary allometric scaling typically used for small-molecule pharmaceuticals.

To provide additional information about preclinical program objectives, selection of suitable animal species and animal models of disease, and overall considerations for the design of preclinical studies to support early-phase clinical trials, FDA has published the guidance entitled “Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products” dated November 2013 (Ref. 3).

IV. CLINICAL TRIAL DESIGN

This section describes specific elements of the design of an early-phase trial for a CGT product. For the most part, this guidance does not discuss elements of the trial design, such as efficacy endpoints and the analysis plan, that are generally the same for CGT products and other types of products. Instead, the discussion focuses on aspects of early-phase clinical trial design that are often different for CGT products than for other types of products. Due to the wide variety of CGT products and their potential applications, a case-by-case assessment is warranted for the design of each clinical trial. Therefore, OCTGT encourages prospective sponsors to meet with FDA review staff early in a development program (see Section V).

A. Early-Phase Trial Objectives

The IND regulations in 21 CFR Part 312 emphasize the importance of the assessment of trial risks and the safeguards for trial subjects. For early-phase clinical trials, especially first-in-human trials, the primary objective should be an evaluation of safety (21 CFR 312.21). Safety evaluation includes an assessment of the nature and frequency of potential adverse reactions and an estimation of the relationship to dose. For CGT products, these early-phase trials often assess not only safety of specific dose regimens and routes of administration, but also other issues, such as feasibility of administration and pharmacologic activity.

Sponsors should consider the design of early-phase studies in the context of the objectives of the overall development program. Therefore, sponsors might include design elements that could help foster further product development. For example, some Phase 1 studies include selected features of Phase 2 study design in order to gather preliminary evidence of effectiveness.

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1. Dose Exploration

For some products and conditions, including many uses of CGT products for serious or life-threatening diseases, some toxicities may be expected and acceptable. In these situations, a major trial objective might be to identify the maximum tolerated dose (MTD), the highest dose that can be given with acceptable toxicity. To achieve this objective, some trials use a well-defined dose-escalation protocol.

For some CGT products, toxicity is not expected to be substantial in the predicted therapeutic range. In this situation, one objective of dose exploration may be to determine the range of biologically active or optimal effective doses. In some cases, indicators of potential benefit may appear to plateau above a certain dose, so that further dose escalation to reach an MTD may seem unnecessary. Although identifying an MTD may seem unnecessary or impractical, it is important to recognize that the effective clinical dose is difficult to estimate early in development. Failure to identify an MTD during early development may lead to subsequent clinical trials using sub-therapeutic dose levels. Therefore, dose exploration that includes identification of the MTD is generally recommended.

Alternatively, for many CGT products, there are significant practical limits on the dose of the product that can be produced or delivered. In such cases, the trial objectives may only be able to focus on achieving a specified target range of exposure or characterizing the safety profile of the feasible dose or doses, rather than finding the MTD.

For further discussion of considerations relating to dose, see Section IV.D.

2. Feasibility Assessments

CGT products sometimes require specialized devices or novel procedures for administration, customized preparation of products, special handling of products (e.g., very short expiration time), or adjunctive therapy. In these cases, sponsors should consider designing early-phase trials to identify and characterize any technical or logistic issues with manufacturing and administering the product. Such issues may need to be addressed before proceeding with further product development.

3. Activity Assessments

A common secondary objective of early-phase trials is to obtain preliminary assessments of product activity, using either short-term responses or longer-term outcomes that could suggest potential for efficacy. Such proof-of-concept data can support subsequent clinical development. For CGT products, activity assessments might include specialized measures such as gene expression, cell engraftment, or morphologic alterations, as well as more common measures such as changes in immune function, tumor shrinkage, or physiologic responses of various types.

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B. Choosing a Study Population

Choice of the subjects to include in the trial depends on the expected risks and potential benefits, recognizing that there will be considerable uncertainty about those expectations in an early-phase trial. Expected risks may be estimated from the nonclinical data, an understanding of the biological mechanisms, and any previous relevant human experience, but the clinical significance of those risks can depend on the population that receives the product. Similarly, the potential for benefit might depend on the choice of study population. In addition, the choice of study population may affect the ability to detect the product's activity, either adverse or beneficial. For example, a biomarker that may be indicative of risk or benefit might be more sensitive, meaningful, or interpretable in one population versus another. Some populations may offer advantages (e.g., higher cell numbers or viability) as sources for autologous products. The objective is to select a trial population with an acceptable balance between the anticipated risks and potential benefits for the study subjects, while also achieving the study's scientific objectives. As discussed below in Section IV.E.4 of this guidance, there are special considerations regarding selection of the study population for patient-specific products.

1. Healthy Volunteers²

Study of healthy adult volunteers may be reasonable for an early-phase trial for products with short duration of action or in a class with a well understood safety profile. However, the risks of most CGT products include the possibility of extended or permanent effects, along with the risks of any invasive procedures necessary for product administration. Therefore, for most CGT trials, the benefit-risk profile is not acceptable for healthy volunteers.

2. Disease Stage or Severity

Selection of the most appropriate study population for an early-phase trial involves several considerations, including not only the potential risks, but also the potential benefits and the ability of the study population to provide interpretable data.

Subjects with more severe or advanced disease may be more willing to accept the risks of an investigational CGT product, or they may be in situations where the risks can be more readily justified. Therefore, sponsors sometimes propose to limit enrollment into early-phase trials to subjects with more severe or advanced disease. However, in some cases, selection of subjects with less advanced or more moderate disease may be appropriate.

Subjects with minimal reserve of physiological function due to severe or advanced disease may be less able than subjects with less severe disease to tolerate additional loss, which could leave them with no function. For example, the risk of a decrease in visual acuity might be more acceptable in a subject with some visual reserve than in a

² For the purposes of this guidance, the term *healthy volunteers* means individuals who do not have the disease or condition of interest.

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subject for whom that same decrement might result in loss of all functional vision. Similarly, a risk of pulmonary or cardiovascular toxicity might be more acceptable in a subject with early lung disease than in a subject with more advanced disease and less pulmonary reserve. In addition, subjects with severe or advanced disease may not be able to tolerate invasive procedures needed for manufacture (e.g., cell harvest) or delivery of the product. Thus, the decision about the severity of disease to be studied in an early-phase trial should be made only after considering the estimated nature and magnitude of the risks to the subjects, and the implications of those risks, for various stages or severity of the disease.

In addition to considerations regarding risks, assessment of the overall benefit-risk profile should take into account any potential for individual subject benefit. In some situations, such as trials in children or trials that involve high-risk procedures, the prospect for individual clinical benefit may be an important factor in the overall benefit-risk assessment for the selected study population. The estimated prospect for benefit may depend on the severity or stage of disease. Although subjects with more severe or advanced disease may have the greatest need for benefit, there can be situations in which a greater potential for benefit might be expected for subjects who are less severely affected. Further, the ability to detect evidence of any benefit could depend on the severity or stage of disease in the study population, and the anticipated effects of the product might be more clearly discernible in subjects with milder disease. This could be a significant consideration if detecting evidence of treatment activity is important to the objectives of the study.

Also, the study population should be chosen with consideration of the potential interpretability of study outcomes. Subjects with severe or advanced disease might have confounding adverse events or be receiving concomitant treatment, related to underlying disease, that could make the safety or effectiveness data difficult to interpret. If the ultimate target population is patients with milder disease, a trial in severe or advanced disease could be essentially uninformative regarding relevant safety information and might also have a smaller prospect for benefit to offset risks.

Thus, while severely affected subjects are often included in early-phase CGT trials, they should not be an automatic choice. Several factors should be taken into account when selecting the appropriate subjects to include in the study for a specific condition. The study population should be chosen in light of the above considerations, and the choice should be discussed and justified in the IND submission.

3. Lack of Other Treatment Options

Early-phase studies of CGT products typically have significant risks and an uncertain potential for benefits. Therefore, early-phase CGT trials sometimes enroll only the subset of subjects who have not had an adequate response to available medical treatment or who have no acceptable treatment options. If a trial is designed to enroll only subjects for whom no other treatment options are available or acceptable, the

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trial should include procedures to ensure that each subject's treatment options have been adequately evaluated, and it should be designed to capture the pertinent information regarding that evaluation.

4. Other Considerations

There are additional considerations for selecting the subject population for certain product types. For example, for cancer vaccines, it may be important to identify subjects whose tumors express a specific target antigen.³ For certain gene therapies, pre-existing antibodies to either the vector or the transgene product may influence the safety or effectiveness of the product; therefore, the study might exclude subjects with such antibodies.⁴ For products for indications (e.g., severe renal, hepatic, or cardiac disease) that might ultimately be amenable to organ transplantation, sponsors should consider whether exposure to the investigational agent would cause sensitization that could compromise the prospect for future transplant success. If so, early-phase trials might exclude subjects with the most imminent or predictable need for transplantation. The exclusion could be reconsidered for subsequent trials once the likelihood of sensitization is better understood.

5. Pediatric Subjects

Some CGT products are developed specifically for pediatric conditions. For example, GT products might be intended to correct childhood genetic diseases by replacing a missing gene or complementing a defective one. CT products might be intended as regenerative medicine to correct congenital deformities or as treatments for genetic diseases, such as hematologic or immunologic disorders, which result in abnormal cellular function.

Sponsors who are developing CGT products to treat pediatric diseases should consider how they will incorporate the additional safeguards for pediatric subjects in clinical investigations into the overall development program. Clinical development programs for pediatric indications usually obtain initial safety and tolerability data in adults before beginning studies in children (Ref. 9). Title 21 CFR Part 50 Subpart D (Subpart D) provides additional safeguards to children in clinical investigations. A detailed discussion of the individual provisions of Subpart D is beyond the scope of

³ “Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines” dated October 2011, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM278673.pdf>.

⁴ In those cases where a special test, such as an antigen or antibody assay, could be critical to the safety or potential effectiveness of the product, the test might be regarded as a companion diagnostic product. If the specific use of the test is also investigational, then the Center for Devices and Radiological Health may need to evaluate the risk of that use. For additional information regarding companion diagnostics, please see the guidance document entitled “In Vitro Companion Diagnostic Devices – Guidance for Industry and Food and Drug Administration Staff” dated August 2014, <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>.

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this guidance, and the FDA has published other documents for that purpose (Refs. 9, 10). We highlight the following principles for sponsors and investigators who wish to conduct studies of CGT products in pediatric subjects.

Before a clinical trial that meets all other applicable requirements may proceed in children, Subpart D requires the Institutional Review Board (IRB) to determine that the trial meets additional requirements applicable to studies in pediatric subjects. The IRB must assess the level of risk that the interventions and procedures included in a clinical trial would present to pediatric subjects to determine whether they present minimal risk (21 CFR 50.51), greater than minimal risk (21 CFR 50.52), or a minor increase over minimal risk (21 CFR 50.53). Because of the special features of CGT products described earlier in this guidance, trials of CGT products usually present more than a minor increase over minimal risk, and therefore would need to meet the requirements of 21 CFR 50.52.

Clinical trials presenting greater than minimal risk may proceed only after the IRB finds either that the intervention or procedure presenting that risk holds out the prospect of direct benefit for the individual pediatric subjects, or that the monitoring procedure presenting that risk is likely to contribute to the subject's well-being. In addition, the IRB must find that:

- the risk is justified by the anticipated benefit to the subjects;
- the relation of the anticipated benefits to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians (21 CFR 50.52 and 50.55).

When an IRB determines that existing data are inadequate to support the findings required under these regulations, it may not permit the study to proceed.⁵

IND submissions for pediatric trials must provide additional information related to plans for assessing pediatric safety and effectiveness (21 CFR 312.23(a)(10)(iii)). The IND regulations also require the sponsor to submit to FDA an investigational plan, including the rationale for the drug or the research study (21 CFR 312.23(a)(3)(iv)(a)). Accordingly, the sponsor should provide a rationale for conducting the CGT study in children. To obtain the information necessary for a benefit-risk assessment under Subpart D, and because of considerations regarding informed consent, data to support the rationale are usually obtained in adults before

⁵ If an IRB cannot conclude that a study meets the requirements of 21 CFR 50.51, 50.52, or 50.53, but finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB may refer the clinical protocol to FDA's Office of Pediatric Therapeutics for review under 21 CFR 50.54. For additional information on this issue, please refer to the FDA guidance entitled "Guidance for Clinical Investigators, Institutional Review Boards and Sponsors - Process for Handling Referrals to FDA Under 21 CFR 50.54 - Additional Safeguards for Children in Clinical Investigations" dated December 2006, <http://www.fda.gov/RegulatoryInformation/Guidances/ucm127541.htm>.

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initiating pediatric studies. We recognize that in some situations, it may be appropriate to initiate clinical studies of CGT products in children based only on the results of preclinical studies. If the sponsor intends to conduct a pediatric trial when there has been no prior safety or efficacy study in adults, the rationale should explain why prior adult studies are unethical or infeasible. For example, the common childhood form of the disease may have severe manifestations or a rapidly deteriorating clinical course, whereas the adult-onset phenotype may be very mild and easily managed. In such a situation, if the intervention is highly invasive, the overall benefit-risk assessment for a study in adults might be so unfavorable that an adult trial to assess safety or efficacy is unethical. In other cases, the disease may occur so rarely in adults that a study in affected adults would not be feasible, and studies in healthy adults might have an unacceptable overall balance of benefits and risks (see Section IV.B.1).

FDA has a responsibility to assess the risks presented and determine whether the clinical trial presents an unreasonable risk to subjects (21 CFR 312.42(b)(1)(i), 312.42(b)(1)(iv) and 312.42(b)(2)(i)). When reviewing studies of CGT products proposed to be conducted in pediatric subjects, we intend to assess the reasonableness of the risks after full consideration of the information, including information relevant to the determinations that the IRB must make to comply with the Subpart D safeguards. The IND submission must provide adequate information to permit FDA to make this assessment (21 CFR 312.23(a)(10)(iii) and 312.23(a)(11)). For example, if the sponsor proposes that a study in pediatric subjects meets the criteria in 21 CFR 50.52 because, among other things, it presents a prospect of direct benefit to the subjects, the sponsor should include the available adult human and animal data relevant to this determination in the IND submission, and an analysis of the balance of anticipated benefit(s) and risks. In addition to providing the relevant animal or adult human data, the IND submission should include a discussion of how those data are sufficient to support an assessment that the pediatric study, taking into account the proposed starting dose, dosing regimen, and design, offers a prospect of direct benefit. FDA may place on clinical hold an IND that does not provide the information FDA needs to assess the risks presented to pediatric subjects (21 CFR 312.42(b)(1)(iv) and (b)(2)(i)).

Finally, in accordance with 21 CFR 312.23(a)(11), the sponsor also must provide the parent or guardian permission document and a child assent document required under 21 CFR 50.55.

C. Control Group and Blinding

The objectives of early-phase trials usually focus on safety, for which rigorous inference regarding comparison to a control (e.g., placebo) may not be necessary. Assessments of activity or efficacy, if any are to be made, are usually exploratory. Therefore, in early-phase trials, a concurrent control group and blinding are generally not as critical as for a

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confirmatory efficacy trial. However, in early phases of clinical development, a control group can be useful to facilitate interpretation of the safety data and provide a comparator for any assessments of activity or efficacy.

For example, a concurrent control group may be particularly valuable for trials in diseases for which the natural history is not well-characterized or for trials that enroll subjects with a wide range of disease severity. The importance of concurrent controls and blinding in any specific trial depends on multiple factors, including not only the study objectives, but also the extent to which the study procedures and outcome assessments are subject to bias.

For some CGT products, use of an intra-subject control may be a useful and convenient way to control a trial. An example would be injection of the study agent into one limb and injection of the control agent into the contralateral limb. With intra-subject control, any systemic effects may confound the interpretation of the results, but comparisons of local effects can be facilitated by the elimination of inter-subject variation.

Standard-of-care and no-treatment controls allow evaluation of the risk of the overall investigational treatment, including the risks of both the study agent and the administration procedure. With this type of control, blinding of the subject and investigator may not be feasible, although it may be possible to maintain the blind for subjects for some kinds of standard-of-care controls.

For trials that do include a concurrent control group, blinding of subjects, investigators, and assessors can be useful to minimize the risk of bias in the study results. However, rigorous blinding in early-phase trials may not be desirable if it cannot be done simply and in a way that minimizes risk to control subjects. Some CGT products might require an invasive procedure for administration (e.g., cardiac catheterization) or for collection of tissue to use for starting materials. Use of the same invasive procedure in a control group could help to distinguish product-related from procedure-related adverse reactions. However, use of the invasive procedure in the control group solely to administer a placebo, or otherwise mimic the active treatment arm for purposes of blinding, could represent an unreasonable risk for an early-phase trial, even if it might be appropriate for a later confirmatory trial. For early-phase clinical trials involving children, the use of an invasive procedure in the control group should present no more than a minor increase over minimal risk, given the absence of a prospect of direct benefit from the control intervention.

Thus, the advantages and disadvantages of specific controls and blinding should be carefully considered in the context of the objectives and circumstances of the specific early-phase clinical trial.

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D. Dose and Regimen

1. Role of Preclinical Data

If animal or in vitro data are available, there might be sufficient information to determine if a specific starting dose has an acceptable level of risk. However, conventional allometric scaling methods for CGT products may be less precise than for small-molecule drugs, and traditional PK and pharmacodynamic correlations might not be possible. Therefore, it may be difficult to establish an initial starting dose based on the considerations used for small-molecule drugs. If available, previous clinical experience with the CGT product or related products, even if by a different route of administration or for a different condition, might help to justify the clinical starting dose.

2. Considerations Regarding How Dose is Described

One of the objectives of early-phase trials should be the identification of the product attribute (or attributes) that is most relevant to characterizing dose. To that end, it is important to collect data on characteristics of the administered product and clinical outcomes that will enable correlative analyses to help in dose definition.

Selecting the study dose(s) of a CT product can be challenging. Dosing to target a therapeutic effect might be based on one cell type, but adverse reactions might depend more on a different cell type that is present in the same product. The active cell subset may not be known, so the dose is based on a specific subset that is thought to be the best representation of the desired activity. For example, for a CT product derived from cord blood or other hematopoietic tissues, the total number of nucleated cells might be used as the measure of dose, but the number of CD3+ cells could be an important aspect of the dose for consideration of certain safety outcomes, such as graft versus host disease (GVHD). In situations where there is uncertainty about the cell subset(s) responsible for the therapeutic or adverse effects, collecting data on various cell subsets in the final CT product, with a comparison of clinical outcomes associated with these different subsets, may help to identify the cell subsets most relevant to product safety and effectiveness.

For many GT products, dose is based on vector titer. However, some vector types may have specific properties that necessitate dosing using alternative units. For example, viral particles that do not contain the therapeutic gene are unlikely to have therapeutic activity. However, these particles themselves might produce adverse reactions, such as an allergic response. Therefore, if there are such safety considerations, the study dose(s) should be based on the total particle number, as is the case with adenoviral vectors. Other considerations for describing dosing may be related to the strengths and weaknesses of the methods available to accurately quantify specific attributes of the GT products. For example, adeno-associated viral

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(AAV) vectors are typically dosed based on vector genomes, due to the strengths of the quantitative polymerase chain reaction (PCR) assay and the difficulties in quantitating transducing units.

For gene-modified cells, dosing should consider several factors, including transduction efficiency. For some products, transduction efficiency can vary from lot to lot. This variation might lead to substantial differences in the active dose administered to different subjects. Ideally, manufacturers should work to control variability in the transduction process. If variability in transduction is occurring, and if the transduced cell number can be identified prior to product administration, then transduced cell number might provide more consistent dosing among subjects. In addition to transduction efficiency, other factors that should be considered in determining the dose include the total number of cells administered to subjects, the mean number of copies of vector sequences integrated per cell, and cell viability.

3. Dose Escalation and Regimen

Clinical development of CGT products has often included dose escalation in half-log (approximately three-fold) increments. However, the dosing increments used for dose escalation should consider preclinical and any available clinical data regarding the risks and activity associated with changes in dose.

Many CGT products can persist in the subject or have an extended duration of activity, so that repeated dosing might not be an acceptable risk until there is a preliminary understanding of the product's toxicity and duration of activity. Therefore, most first-in-human CGT trials use a single administration or one-time dosing regimen. However, for some CGT products, such as therapeutic vaccines, multiple administrations may be appropriate for early-phase trials.

E. Treatment Plan

1. Staggering Administration

When there is no previous human experience with a specific CGT product or related product, treating several subjects simultaneously may represent an unreasonable risk. To address this issue, most first-in-human trials of CGT products include staggered treatment to limit the number of subjects who might be exposed to an unanticipated safety risk.

With staggered treatment, there is a specified follow-up interval between administration of the product to a subject, or small group of subjects, and administration to the next subject or group of subjects. For example, in a dose-escalation study, the first several individual subjects within the first cohort might be staggered, followed by staggering between cohorts. Depending on the degree of safety concern, staggered treatment of individual subjects within each new cohort

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might be appropriate. When the dose of the CGT product is difficult to quantify precisely or is highly variable due to manufacturing issues, it may be necessary to stagger additional subjects.

The staggering interval, either within a cohort or between cohorts, is intended to be long enough to monitor for acute and subacute adverse events prior to treating additional subjects at the same dose, or prior to increasing the dose in subsequent subjects. The choice of staggering interval should consider the time course of acute and subacute adverse events that was observed in the animal studies and in any previous human experience with related products. The staggering interval should also consider the expected duration of product activity. However, the staggering interval should be practical in the context of overall development timelines.

2. Cohort Size

For trials that enroll sequential cohorts with dose-escalation between cohorts, the choice of cohort size should consider the amount of risk that is acceptable in the study population. Larger cohorts might be necessary to provide reasonable assurance of safety before escalating the dose of a product intended to treat a disease that is less serious and for which the tolerance for accepting risk might be lower. Smaller cohorts might be adequate for a product that is intended to treat a serious or life-threatening disease where a greater potential benefit may justify a higher risk. Standardized protocol designs, such as the 3+3 design, are often used for dose escalation of oncology products. However, the cohort size in such a design might not be appropriate for other therapeutic areas where there is less tolerance of risk, and a larger cohort might be needed to provide a greater assurance of safety prior to dose escalation. In addition, other study objectives, such as assessments of tolerability, feasibility, and pharmacologic activity may influence choice of cohort size.

For CGT products, manufacturing capacity is often limited, which might place a practical limit on cohort size, particularly early in clinical development. The prevalence of the proposed study population may also limit the cohort size. When considering the limitations due to manufacturing capacity and prevalence of the study population, sponsors should select a cohort size that is feasible, but still adequate to meet the study objectives.

3. Operator Training and Documentation of Procedures

For product delivery that involves a complex administration procedure or a device requiring special training, such as subretinal injection or use of specialized catheters for cardiac administration, the skill of the individual administering the product can impact the product's safety and efficacy. When individual skill in administering a product may affect its safety or effectiveness, the trial should specify minimum requirements for the operator's training, experience, or level of proficiency. In some cases (particularly, if there are multiple operators), training of operators on the specific administration procedures may reduce variability of administration and

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thereby improve interpretability of the study results. Detailed, written standard operating procedures (SOPs) can also help ensure safety and consistency in product administration. Careful recording of steps and observations during the administration process can help identify the operator's compliance with the protocol. These records can also facilitate correlating procedure variations with clinical outcomes and identify modifications that may improve the administration process.

4. Considerations for Patient-Specific Products

As discussed earlier, some CT products or gene-modified cells are manufactured using cells or tissue from the intended recipient or from an allogeneic donor selected because of immunological matching to the recipient. In these cases, the product needs to be manufactured separately for each subject in a trial.

However, manufacturing of some CGT products may take many weeks or months. Although a subject might meet the study enrollment criteria when the tissue or cells are first collected, the subject might no longer meet those criteria at the time planned for product administration. For example, the subject's condition may have deteriorated so that the subject is no longer expected to tolerate the study procedures or survive for the study duration. To adjust for the possibility of a change in the subject's condition, the enrollment criteria may need to include selection for factors that would improve the likelihood that the recipient would still be suitable for product administration when the manufacturing process is complete. Alternatively, the trial might include separate criteria that need to be met at the time of product administration.

If a problem occurs in product manufacturing, there may be no product available to administer to an intended recipient. It is helpful to try to gain an understanding from early-phase trials of the likelihood of manufacturing failure and any subject factors that may relate to such failures (e.g., subject characteristics that might predict a poor cell harvest). This information can facilitate design of subsequent trials by suggesting subject selection criteria to reduce the chance of failure, or by prompting the development of a treatment protocol with a formalized manufacturing failure contingency plan.

In case of failure to administer the CGT product to a subject, the protocol should be designed so that the subject is not committed to any high-risk preparative procedures (e.g., myeloablation) until it is known that the product is available. The protocol should also clearly specify whether re-treatment will be attempted with another round of manufacturing and whether an untreated subject will be replaced by increasing enrollment. Failure-to-treat may be an important trial endpoint that is part of a feasibility evaluation, and there should be plans to analyze the proportion of failure-to-treat subjects to look for factors that may predict failure to administer the product and to evaluate the consequences to the subject if there is a failure to treat.

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F. Monitoring and Follow-up

1. General Monitoring Considerations

Since a major objective of early-phase trials is evaluation of safety, early-phase trials should employ general tests and monitoring to look for both expected and unexpected safety issues. General safety monitoring typically includes recording of symptoms and common clinical measurements, such as physical examinations, chemistry profiles, complete blood counts, and possibly other examinations that are appropriate for the condition being investigated. Examples include continuous electrocardiographic monitoring if arrhythmogenicity is a concern, and antinuclear antibody (ANA) or other immunology testing if autoimmunity is a concern. The specific monitoring program will depend on multiple factors, such as the nature and mechanism of action of the product, the study population, the results of animal studies, and any related human experience.

Another objective of many early-phase trials is to provide preliminary evidence of efficacy or pharmacologic activity. Pharmacologic activity may develop slowly or be delayed relative to the traditional time course of activity of small molecules. Therefore, subjects should continue to be monitored for both safety and pharmacologic activity regardless of whether or not they receive the complete treatment regimen.

Attribution of individual adverse events to the product, study procedures, or other causes can be unreliable. Therefore, for early-phase trials, sponsors should capture all adverse events, even if the investigational product is an add-on to known toxic therapies, such as chemotherapy, radiation, or another toxic drug. Many early-phase CGT trials include a Data Monitoring Committee (DMC) to help ensure subject safety. Although use of a medical monitor may be sufficient, a DMC might be considered to enhance subject protection if the trial presents substantial risks to subjects.⁶

In addition to providing evidence of safety, many early-phase clinical trials have the secondary objective of obtaining preliminary efficacy or proof-of-concept data to support subsequent clinical development. Therefore, sponsors are encouraged to include a wide range of activity or efficacy outcome measures in early-phase clinical trials.

2. Special Monitoring Considerations for CGT Products

In addition to general tests and monitoring to look for unanticipated safety issues, evaluations may include assessments targeting specific safety issues that could be anticipated with CGT products. Such product-specific safety issues might include

⁶ For additional information on DMCs, please see the guidance document entitled “Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees” dated March 2006, <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf>.

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acute or delayed infusion reactions, autoimmunity, graft failure, GVHD, new malignancies, transmission of infectious agents from a donor, and viral reactivation. Monitoring procedures relevant to specific CGT products or study populations include the following:

- If immunogenicity is a concern (e.g., with viral capsids or allogeneic cellular products), then each subject's immune response to the product should be evaluated. This evaluation may include monitoring for evidence of both cellular and humoral immune responses. If adequate assays are not yet available, baseline and post-treatment blood and/or plasma, as appropriate, should be cryopreserved for later evaluation, once assays have been developed.
- Attempts should be made to determine the duration of persistence of the product and its activity. Product persistence is assessed by looking for evidence of the presence of cells, vector, or virus in biological fluids or tissues. Activity might be assessed by looking for physiologic effects, such as gene expression or changes in biomarkers. In some trials, these assessments of persistence or activity could be based on relevant tissue (e.g., from the site of administration or the site of intended activity) that becomes available in the course of subject management or is easily obtained by biopsy. In such trials, the protocol might include plans for tissue studies. If some deaths are expected to occur during the course of the trial, planning for possible postmortem studies to assess product persistence and activity may be useful.
- For CT products, if applicable, the potential for migration from the target site, ectopic tissue formation, or other abnormal cell activity should be addressed by performing evaluations appropriate to the nature of the concern (e.g., imaging studies for potential ectopic tissue, or cardiac rhythm monitoring for potential arrhythmogenic foci in cardiac disease).
- For GT products, the potential for viral shedding should be addressed early in product development.^{7,8}
- For GT products that integrate into the genome, monitoring for clonal outgrowths should be performed when technically feasible. Typically, this type of monitoring is done when hematopoietic stem cells are transduced with an integrating vector. Vector integration sites in patient peripheral blood

⁷ "Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors" dated October 2006, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072961.htm>.

⁸ "Draft Guidance for Industry: Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products" dated July 2014, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm404050.htm>. When finalized, this guidance will represent FDA's current thinking on this topic.

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mononuclear cells (PMBCs) can be monitored for outgrowth of a predominant clone. Additional information can be found in the “Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events” dated November 2006 (Ref. 11).

- CGT products may affect linear growth and maturation of developing organ systems in children. The systems that are most likely to be affected may vary by product, but concerns include potential reproductive, immunologic, neurologic, skeletal, or psychological effects. Therefore, monitoring and assessment of effects on these systems may be critical elements in the design of pediatric clinical trials.

3. Duration of Follow-up

In general, the duration of monitoring for adverse events should begin with any pretreatment and cover the time during which the product might reasonably be thought to present safety concerns. In addition, the expected time course of pharmacologic activity may influence the duration of monitoring. The appropriate duration of follow-up depends on the results of preclinical studies, experience with related products, knowledge of the disease process, and other scientific information. In case of failure to administer the CGT product to a subject, the protocol should stipulate any follow-up time needed to assess the risks of any harvesting procedure or other type of preparative treatments (e.g., immune modification) the subject received.

For most CGT products, a year or more of follow-up is appropriate for each subject in early-phase trials. For some CGT products, such as those with an indefinite duration of activity, additional long-term follow-up might be appropriate. For example, long-term safety monitoring can be useful if the product contains cells for which there is concern, either from the animal studies or other scientific information, that the cells might transform, migrate, or otherwise have the potential to develop ectopic tissue. The monitoring program should account for the duration of risks due to any concomitant medications, such as immunosuppressants. In addition, sponsors should consider the duration of follow-up that will provide preliminary evidence of efficacy and information on durability of activity.

With respect to extended follow-up, for certain GT products, we recommend following the recommendations in the FDA guidance document entitled “Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events” dated November 2006 (Ref. 11). As stated in that guidance, if the product is a GT for which the vector is integrating, or if the vector has latency, such as herpes simplex virus, then sponsors should follow subjects for 15 years to identify any late safety issues. Long-term safety monitoring can also be useful if the product involves a gene that might predispose subjects to develop secondary malignancies.

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Sponsors sometimes propose to have one protocol for a CGT study of safety or efficacy, and a separate protocol for long-term monitoring. However, long-term follow-up is sometimes necessary for the trial to have an acceptable balance of risks and benefits. In that case, long-term monitoring should be included as an integral part of the CGT trial, and not designed as a separate study. There may be logistical issues that influence the feasibility of including long-term monitoring in the initial protocol. When there is a separate protocol for long-term monitoring, subjects should be consented for all long-term monitoring prior to participation in the initial CGT trial.

Long-term monitoring does not need to be as detailed as the safety monitoring in the initial part of a trial. In general, long-term monitoring for CGT products focuses on subject survival and on serious adverse events that are hematologic, immunologic, neurologic, or oncologic. For some purposes, a telephone call to the subject, rather than a clinic visit, may be sufficient to obtain the necessary follow-up information. In addition, completion of long-term monitoring usually is not necessary prior to initiating subsequent trials or submitting a marketing application.

In the pediatric population, long-term monitoring following the administration of CGT products may need to characterize the effects of the intervention on growth and development as discussed in Section IV.F.2 of this guidance. Depending on the intervention, children also have the potential to be exposed for a longer time because of their younger age. Thus, clinical follow-up data over an extended period may be critical to assess safety and developmental outcomes, particularly when an intervention is tested in infants and young children. Therefore, monitoring the long-term safety and duration of effects may be more challenging in pediatric studies than in adult studies. Sponsors of all CGT early-phase trials, both adult and pediatric, should consider these issues in their proposals for long-term monitoring.

4. Study Stopping Rules

Because there can be considerable uncertainty about the frequency or severity of adverse reactions in trials of CGT products, most early-phase trials of these products should include study stopping rules. The purpose of these rules is to control the number of subjects put at risk, in the event that early experience uncovers important safety problems.

Study stopping rules typically specify a number or frequency of events, such as serious adverse events or deaths, that will result in temporary suspension of enrollment and dosing until the situation can be assessed. Based on the assessment, the clinical protocol might be revised to mitigate the risk to subjects. Such revisions could include changes in the enrollment criteria, for example, to exclude individuals who might be at relatively high risk for developing particular adverse reactions. Revisions might also include dose reduction, some other change in product preparation or administration, or changes in the monitoring plan. Following the implementation of such changes in the protocol, it may be safe for the trial to resume.

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Therefore, study stopping rules do not necessarily terminate a trial. Well-designed stopping rules allow sponsors to assess and address risks identified as the trial proceeds, and to assure that risks to subjects remain reasonable.

V. MEETINGS WITH OCTGT

OCTGT encourages prospective sponsors to meet with FDA review staff. Meeting with OCTGT can be especially beneficial for sponsors who have little experience with the IND process, and for sponsors developing a product for the treatment of a rare disease. In such meetings, OCTGT can provide advice that may increase the likelihood that an IND submission will be sufficient to support a proposed trial, or that the overall development program will be sufficient to support a marketing application.

The FDA guidance document entitled “Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants” dated May 2009 (Ref. 12), describes the process for requesting and preparing for a meeting. One type of formal meeting is the pre-IND meeting. A pre-IND meeting is intended to help ensure that appropriate work has or will be done to support a planned IND. The sponsor’s pre-IND briefing package should include a clinical protocol or synopsis. In addition to discussions of preclinical studies and manufacturing issues, appropriate clinical topics for such a meeting could include the following:

- the adequacy of the available or planned safety and proof-of-concept information to justify the risks of the proposed trial;
- the choice of study population;
- the doses to be administered;
- the dosing schedule;
- clinical issues related to any invasive administration procedures;
- the treatment plan for the control group, if one is proposed;
- staggering plans;
- the safety monitoring plan, including long-term follow-up;
- any special safety assessments;
- stopping rules;
- selection of trial endpoints; and
- the overall clinical development program.

VI. GUIDANCE ON SUBMITTING AN IND

The requirements with respect to what needs to be submitted in support of an IND can be found in the FDA regulations, 21 CFR 312.23, and recommendations with respect to these submissions can be found in the FDA guidance document entitled, “Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products” dated November 1995 (Ref. 13). Information on the preparation of the CMC section of an IND for a CGT product can be found in the FDA guidances entitled “Guidance for FDA Reviewers and Sponsors:

Contains Nonbinding Recommendations

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)” dated April 2008 (Ref. 1) and “Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)” dated April 2008 (Ref. 2). As noted previously, information on the preparation of the preclinical section of an IND for a CGT product can be found in the FDA guidance entitled “Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products” dated November 2013 (Ref. 3).

The IND submission for an early-phase trial must include a summary of previous human experience known to the applicant with the investigational product, along with detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigator’s rationale (21 CFR 312.23(a)(9)). The submission also should include a summary of previous human experience with similar or closely related products. OCTGT recommends that the submission include discussion of any of the issues raised in Sections III and IV of this guidance that are applicable to the proposed trial.

Sponsors also may find it prudent to develop an overall product development plan early in the course of development (prior to clinical trial initiation). Such a plan should be sufficiently flexible to accommodate adaptation based on data acquired through product development. One potential approach to planning development is known as a Target Product Profile (TPP). FDA has published a draft guidance for comment that discusses how this particular planning tool might be used (Ref. 14). When finalized, the TPP guidance will represent our current thinking on this topic.

FDA has developed additional resources that sponsors may find useful when preparing an IND for CGT products, including guidances relevant to the development of CGT products for selected specified conditions.^{3,9,10,11} Likewise, information on manufacturing, preclinical, and clinical topics related to development of CGT products, including discussion of IND submissions and meeting requests, is available in the OCTGT Learn webinars on the OCTGT website: <http://www.fda.gov/biologicsbloodvaccines/newsevents/ucm232821.htm>.

⁹ “Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products” dated September 2009, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm182440.htm>.

¹⁰ “Guidance for Industry: Cellular Therapy for Cardiac Disease” dated October 2010, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm164265.htm>.

¹¹ “Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage” dated December 2011, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM288011.pdf>.

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Contains Nonbinding Recommendations

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