

Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2013**

Contains Nonbinding Recommendations

Draft – Not for Implementation

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.....	7
	C. Control Group and Blinding.....	10
	D. Dose Selection	11
	E. Treatment Plan.....	12
	F. Monitoring and Follow-up	14
V.	MEETINGS WITH OCTGT	18
VI.	GUIDANCE ON SUBMITTING AN IND.....	18
V.	REFERENCES.....	21

Contains Nonbinding Recommendations

Draft – Not for Implementation

Guidance for Industry

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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 of Investigational New Drug Applications (INDs) for cellular therapy (CT) and gene therapy (GT) products. CT and GT products will be referred to collectively as CGT products. This guidance provides recommendations to assist in designing early-phase clinical trials of CGT products. When this guidance is finalized, we believe it will clarify OCTGT's current expectations 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)). 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 Code of Federal Regulations (CFR) Part 1271 (21 CFR Part 1271), 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 IND, as we have previously provided recommendations in connection with these components (Refs. 1, 2)

Contains Nonbinding Recommendations

Draft – Not for Implementation

(Ref. 3, when finalized, will reflect our current thinking on that topic). When finalized, this guidance is intended to complement the information in those guidances.

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.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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 these 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.

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 a single administration, or have an extended duration of 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 might require observation of subjects for a substantial period of time to understand the safety profile.

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. 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 may be investigational, as well, and, as indicated in Section V of this guidance, it is appropriate to discuss clinical issues related to this 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, and we refer you to Section IV.E.4. of this guidance in connection with this issue.

Allogeneic CT products, GT vectors, and proteins that might be produced by CGT products have the potential to elicit an immune response (immunogenicity). Immunogenicity may be significant in one of the two following ways. First, 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. Second, in patients who have a condition that could be treated with a

Contains Nonbinding Recommendations

Draft – Not for Implementation

cellular, tissue, or organ transplant in the future, the development of antibodies to an allogeneic CGT product might jeopardize the prospect for successful transplantation.

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. 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 toxicity 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 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.

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 other 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 tumors. In addition, GT products present the possibility of viral or bacterial 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

Contains Nonbinding Recommendations

Draft – Not for Implementation

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. In addition, cell viability and potency may decline rapidly from the time of formulation. Therefore, “fresh” cells that are not cryopreserved may need to be administered within hours of manufacturing.

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.

C. Preclinical Considerations

Preclinical in vitro and in vivo proof-of-concept (POC), pharmacology, and toxicology studies are conducted to characterize the safety profile of investigational products. 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 risk-benefit analysis, performed in the context of the particular clinical indication 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.

The extrapolation of a potentially safe and possibly bioactive starting clinical dose from the animal data can depend on various factors, such as the animal models used, the anatomic site 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. These issues can limit the ability of the preclinical data to guide various aspects of the design of the early-phase clinical trial.

For additional information about preclinical program objectives, selection of suitable animal species and animal models of disease, and overall considerations for the design of

Contains Nonbinding Recommendations

Draft – Not for Implementation

preclinical studies to support early-phase clinical trials, we note that FDA has published the draft guidance entitled “Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products” (dated November 2012) (Ref. 3). This guidance, when finalized, will represent FDA’s current thinking on this topic.

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.

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 levels, but also other issues, such as feasibility of administration and pharmacologic activity.

1. Dose Exploration

For some products and indications, including many uses of CGT products for 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, the 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 plateau above a certain dose, so that further dose escalation to reach an MTD may be unnecessary.

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 focus on characterizing the safety profile of the feasible dose or doses, rather than finding the MTD.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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. For CGT products, these outcomes 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.

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 by the nonclinical data 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.5 of this guidance, there are special considerations regarding selection of the study population for patient-specific products.

1. Healthy Volunteers

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 persistent or permanent effects, along with the risks of any invasive procedures necessary for product administration. Therefore, for most CGT trials, the risk-benefit profile is not acceptable for healthy volunteers.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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 a situation where the risks can be more readily justified. Therefore, sponsors sometimes propose to limit enrollment in early-phase trials to subjects with more severe or advanced disease. However, in some cases, selection of patients with less advanced or more moderate disease may be more 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 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. 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 risk-benefit 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 benefit may be an important factor in making the risk-benefit 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, due 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

Contains Nonbinding Recommendations

Draft – Not for Implementation

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 indication. 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 present significant risks and an uncertain potential for benefits. Therefore, for any specific target indication, 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 treatment options. When subjects are selected because no other treatment options are available or tolerable, the trial should include procedures to ensure that the lack of treatment options is adequately evaluated, and the protocol should be designed to capture the pertinent information regarding that evaluation.

4. Pediatric Subjects

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

Title 21 CFR Part 50, Subpart D provides additional safeguards to children in clinical investigations. A discussion of the individual provisions of Subpart D is beyond the scope of this guidance, and FDA directs you to other documents for this purpose. (Refs. 9, 10) We highlight the following principles for sponsors who wish to conduct studies of CGT products in pediatric subjects.

Before a trial may proceed, Subpart D requires an assessment of the level of risk that the clinical trial would pose to pediatric subjects (minimal risk, slightly more than minimal risk, or greater than minimal risk) and of the outcome or consequence of the trial (the prospect of direct benefit to subjects, the development of generalizable knowledge about the subjects' disorder or condition, or an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children).

Under 21 CFR 50.50, an Institutional Review Board (IRB) is authorized to approve a clinical trial in children only after assessing the risks and outcome of the planned trial, and finding that the trial meets the requirements of Subpart D. In some

Contains Nonbinding Recommendations

Draft – Not for Implementation

instances, an IRB may determine that additional data from studies in animals or in adults are needed, either as safety data or to support a prospect of direct benefit, before the study may be conducted in children consistent with Subpart D.¹

FDA also has a responsibility to determine whether the study presents an unreasonable risk to subjects (21 CFR 312.42(b)(1)(i) and (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 presented within the context of the Subpart D safeguards. Accordingly, the investigational plan submitted under 21 CFR 312.23 should provide adequate information to permit FDA to make this assessment. For example, when the study would present greater than minimal risk to pediatric subjects, the sponsor should submit to the IND the proof-of-concept data used in support of the prospect of direct benefit. Evidence of a prospect of direct benefit might come from studies in animal models of the disease or condition, or from initial clinical studies in adults.

C. Control Group and Blinding

In early phases of clinical development, a control group can be useful to facilitate interpretation of the safety data and provide a comparator for preliminary assessments of activity. A concurrent control group may be particularly valuable for CGT 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. For trials that 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, some CGT products require invasive procedures for administration or for collection of starting materials. In such cases, rigorous blinding in early-phase trials may not be desirable if it cannot be done simply and with minimal risk to control subjects. The primary objective for an early-phase trial should be preliminary assessment of safety, for which rigorous inference regarding comparison to placebo is not usually necessary. Conclusions about efficacy, if any are to be made, are at best exploratory. Therefore, in early-phase trials, blinding is generally not as critical as for a confirmatory efficacy trial. For example, an invasive procedure such as cardiac catheterization may be required to administer the investigational product. Using a similar invasive procedure to administer a placebo to the control group for purposes of blinding could represent an unacceptable risk for an early-phase trial, even if it might be considered for a later confirmatory trial. The risk of the administration procedure is also an aspect of the overall treatment that needs to be evaluated, so a noninvasive control group might be more appropriate in early-

¹ If an IRB cannot conclude that a study meets the requirements of 21 CFR Part 50, specifically 21 CFR 50.51, 50.52, or 50.53, under certain circumstances, 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>

Contains Nonbinding Recommendations

Draft – Not for Implementation

phase trials. The importance of blinding in any specific trial depends on multiple factors, including the extent to which the study procedures and outcome assessments are subject to bias.

D. Dose Selection

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, 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

Contains Nonbinding Recommendations

Draft – Not for Implementation

related to the strengths and weaknesses of the methods available to accurately quantify specific attributes of the GT products. For example, adeno-associated viral (AAV) vectors are typically dosed based on vector genomes, due to the strengths of the quantitative PCR assay and the difficulties in quantitating transducing units.

For gene-modified cells, dosing should take transduction efficiency into account. For gene-modified cells produced by the most current techniques, transduction rates can be as high as 70 to 80 percent. However, transduction rates can be highly variable depending on the product, and rates 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, using the transduced cell number might provide more consistent dosing among subjects when that number can be identified prior to product administration.

E. Treatment Plan

1. Dosing Regimen

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.

2. Staggering Administration

When there is no previous human experience with a specific dose, treating several subjects simultaneously with that dose 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 might be appropriate.

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

Contains Nonbinding Recommendations

Draft – Not for Implementation

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.

3. Cohort Size

For trials that enroll sequential cohorts with dose-escalation between cohorts, the cohort size should depend on 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 for 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 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.

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.

4. 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, prior to participating in the trial. In some cases (particularly, if there are multiple operators), training of operators on the specific administration procedures may reduce variability of administration and thereby improve interpretability of the study results. 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.

Contains Nonbinding Recommendations

Draft – Not for Implementation

5. 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 it (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 clearly specify whether re-treatment will be attempted with another round of manufacturing. The protocol should also identify 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.

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

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

Attribution of individual adverse events 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 subjects².

2. Special Monitoring Considerations for CGT Products

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

² 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>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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 CGT studies).
- For GT products, the potential for viral shedding should be addressed early in product development.³
- 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 be designed to cover the time during which the product might reasonably be thought to present safety concerns. 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 the follow-up time that is still needed to assess the risks of any harvesting procedure or other type of preparative treatments the subject might have 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.

³ 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>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

With respect to extended follow-up, for certain GT products, we recommend you follow 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.

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 protocol.

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 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. 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 stopping rules. The purpose of stopping rules is to control the number of subjects put at risk, in the event that early experience uncovers important safety problems.

Stopping rules typically specify a number or frequency of events, such as serious adverse events or unexpected 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

Contains Nonbinding Recommendations

Draft – Not for Implementation

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. Therefore, 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. In such meetings, OCTGT can provide advice that may increase the chance 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 supporting 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;
- 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 application can be found in the FDA regulations, 21 CFR 312.23, and recommendations with respect to these

Contains Nonbinding Recommendations

Draft – Not for Implementation

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: 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). In addition, as noted previously, the draft guidance entitled “Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products” (dated November 2012) (Ref. 3), when finalized, will reflect our current thinking on this topic.

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, this 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 indications.^{4,5,6,7} Likewise, information on manufacturing, preclinical, and clinical

⁴ Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products; dated September 2009, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm182440.htm>.

⁵ Guidance for Industry: Cellular Therapy for Cardiac Disease; dated October 2010, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm164265.htm>.

⁶ Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines; dated October 2011, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM278673.pdf>.

⁷ 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>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

VII. REFERENCES

1. Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs); dated April 2008, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074131.htm>.
2. 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, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072587.htm>.
3. Draft Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products; dated November 2012, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM329861.pdf>.
4. Raper S.E., N. Chirmule, F.S. Lee, et al., 2003, Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer, *Molecular Genetics and Metabolism*, 80:148-158.
5. Hacein-Bey-Abina S., C. Von Kalle, M. Schmidt, et al., 2003, LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1, *Science*, 302:415-419.
6. Amariglio N., A. Hirshberg, B.W. Scheithauer, et al., 2009, Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient, *PLoS Medicine*, 6(2):221-230.
7. Zhang, Y.M., C. Hartzell, M. Narlow, S.C. Dudley, 2002, Stem Cell-Derived Cardiomyocytes Demonstrate Arrhythmic Potential, *Circulation*, 106:1294-1299.
8. Gu, E., W. Chen, J. Gu, P. Burrige, J. Wu, 2012, Molecular Imaging of Stem Cells: Tracking Survival, Biodistribution, Tumorigenicity, and Immunogenicity, *Theranostics*, 2(4):335-345.
9. Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population; dated December 2000, <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129477.pdf>
10. Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products. 78 FR 12937 (February 26, 2013).

Contains Nonbinding Recommendations

Draft – Not for Implementation

11. Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events; dated November 2006,
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm>.
12. Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants; dated May 2009,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.
13. 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,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf>.
14. Draft Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool; dated March 2007,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080593.pdf>.