Guidance for FDA Review Staff and Sponsors

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Submit comments and suggestions regarding this draft document by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to 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 published in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
November 2004

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GUIDANCE FOR FDA REVIEW STAFF AND SPONSORS

Content and Review of Chemistry, Manufacturing, and Control Information for Gene Therapy Investigational New Drug Applications (INDs)

This guidance represents 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 or 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

A. Why Is CBER Issuing This Guidance?

Human gene therapies present a multitude of manufacturing challenges that must be overcome in order to deliver a safe and effective product. Some of these challenges include the variability and complexity inherent in the components used to generate the final product, such as the source of cells (i.e., autologous or allogeneic), the potential for adventitious agent contamination, the need for aseptic processing, and the inability to "sterilize" the final product since it contains living cells. Distribution of these products can also be a challenge due to stability issues and the potentially short shelf life of many cellular products, often necessitating the need to release the final product for administration to a patient before required test results for lot release are available. This document provides guidance to industry on the chemistry, manufacturing and control (CMC) information to include in an original investigational new drug application (IND). Additionally, this document provides instructions to FDA staff for CMC reviews of human gene therapy on the information to record and assess as part of a review of an original IND, taking into consideration the various manufacturing challenges for these products, such as those mentioned above.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe 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.

B. How Will CMC Reviewers of Gene Therapy INDs and Industry Use This Guidance?

FDA's primary objectives in the review of INDs are to help assure the safety and rights of subjects in all phases of the investigation, and in Phases 2 and 3, to help assure that the quality of the scientific evaluation of the investigational product is adequate to permit an evaluation of its safety and effectiveness (21 CFR 312.22(a)). This guidance will help sponsors and reviewers to assess, given the phase of the investigation, whether sufficient information is provided to assure the proper identification (identity testing), quality, purity, and strength (potency) of the investigational product (21 CFR 312.23(a)(7)(i)). These principles apply to investigational biological products and drugs; however, specific terms, such as safety, identity, purity, and potency, are generally understood to be applicable to biological products and are used throughout this document.

If you are an FDA reviewer, you will use this guidance as you assess the quality of an investigational product and you will use the format of the human gene therapy CMC review template (Appendix A) in preparing your reviews. Because of the wide variability of the contents of IND amendments, you are only expected to use the attached template during review of IND original submissions. However, you should consult this document for guidance throughout the investigational new drug development process.

The human gene therapies CMC review guidance and template described in this document are tools to assist FDA in the review of human gene therapy INDs. They are designed to serve as a guide to help ensure that all applicable regulatory requirements are reviewed at the appropriate stage of product development. In addition to the CMC review instructions and template, some general considerations that should be helpful in assessing proposed release criteria testing and specifications are discussed in Appendix B. Section 10.70, 21 Code of Federal Regulations, provides further instruction to CMC reviewers regarding documentation of review decisions.

If you are a sponsor of a gene therapy IND, you may use this guidance in developing an IND submission that will be adequate to permit FDA staff to make an assessment of the safety and quality of your investigational product. Other regulatory documents that may be relevant are listed in Appendix C.

C. How Is This Guidance Organized?

The guidance is organized in a format that generally corresponds to the sections in the CMC review template provided in Appendix A. In each section, where necessary, we provide recommendations as to the information sponsors may submit in their original IND submissions. As necessary throughout this document, we give specific instructions to CMC reviewers concerning their documentation and assessment of an IND submission during completion of CMC review.

II. ADMINISTRATIVE INFORMATION TO BE DOCUMENTED BY FDA CMC REVIEWERS

CMC Reviewers: Document in your review all of the IND information listed below. Most of this information should be available on Form FDA 1571, the sponsor's cover letter, or the reviewer assignment notice from the application division Regulatory Project Manager (RPM).

- BB- IND Number (assigned by CBER after receipt),
- Date of submission,
- 30 Day review due date,
- Sponsor - name, address, phone, fax,
- Sponsor point of contact (sponsor's authorized representative) - name address, title, phone, fax,
- Title of IND,
- Proposed use,
- Product description,
- Phase of study,
- Cross-referenced INDs, investigational device exemptions (IDEs), and master files (MFs): List all regulatory files (IND, IDE, MF) that the sponsor has obtained permission to cross-reference in support of this file. The file under review must contain a letter signed by the sponsor of the cross-referenced file (21 CFR 312.23(b)), giving permission for the cross-reference. This letter should identify the nature of the information being cross-referenced (e.g., pre-clinical, product manufacturing, and/or clinical) and where it is located within the file being cross-referenced. Verify that the cross-referenced information satisfies the IND requirement for which the information is cited. If the letter of cross-reference is absent or inadequate, or the cross-referenced information is inadequate for the purpose cited, the RPM or the CMC reviewer should notify the sponsor to obtain additional information.
- Key words: Include three to four words that can be used to identify the product, indication, and important reagent or device. These key words should be general enough to be used in a data base search.
- Introduction/rationale: Summarize relevant information on the development of the product if the sponsor provides this information. In addition, document and assess, as appropriate, the sponsor's scientific rationale and justification for using the product for the indication under review, and
- Study objectives.

III. PRODUCT MANUFACTURING AND CHARACTERIZATION INFORMATION TO BE SUBMITTED BY SPONSORS AND DOCUMENTED BY REVIEWERS

As described in the following sections, we recommend that you, a sponsor, provide a detailed description of where and how the gene therapy product is manufactured. Include all of the components used during the manufacture of the gene therapy product, such as vector, cells or cell bank systems, and any reagents or excipients. In addition, describe all procedures used during the manufacturing process. Examples of these procedures may include production and

purification of the vector, preparation of ex vivo gene modified cells, and final formulation of the product. This information will allow us to assess the identity quality, purity, and potency of your product. For further information, refer to the "Guidance for Human Somatic Cell Therapy and Gene Therapy" (Ref. 1), the guidance on "Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products" (Ref. 2). In addition, you may refer to the other final documents listed in Appendix C, and, when finalized and where relevant, the "Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing and Control (CMC) Reviewers of Human Cell Therapy Investigational New Drugs (INDs)" (Ref. 3).

CMC reviewers will document and assess product manufacturing and characterization information in their IND reviews. Reviewers should organize the CMC review using the format and headings described in Appendix A and below, as appropriate.

A. Product Manufacturing – Components

The sections below detail the information on manufacturing components that we recommend that you, a sponsor, submit in an IND, and which CMC reviewers will document and assess. Reviewers should note the source of each component and summarize the testing performed on each component, and review the specific instructions and recommendations set out below.

1. Vector – We recommend that you, a sponsor, provide the following information about your vector:

a. Gene Therapy Vector Construct

A description of the history and detailed derivation of the gene therapy vector including:

- The gene map, with relevant restriction sites, and any vector constructs used during generation of the final vector and their sources
- The gene insert
- Regulatory elements, such as promoter, enhancer, and poly-adenylation signal
- Selection markers

b. Vector Diagram

A diagram of the vector identifying the gene insert and regulatory regions, and any other relevant elements, such as pertinent restriction endonuclease sites:

CMC Reviewers: You may document the vector diagram by scanning it into the review document.

c. Sequence Analysis

Vectors 40kb or less: We recommend that you, a sponsor, fully sequence all vectors under 40 kilobases (kb) and that you describe how the sequence analysis was performed. We further recommend that you summarize the sequence annotation, indicating the identity of all open reading frames (expected and unexpected) and genes encoded in the vector. Indicate whether there is sequence alignment between the vector and sequences identified by a search in a relevant current database.

Vectors greater than 40kb: We recommend that you, a sponsor, summarize the extent and results of sequence analysis that you have performed including any testing performed by restriction endonuclease analysis. We recommend that you perform sequence analysis of the gene insert, flanking regions, and any regions of the vector that are modified.

2. Cells

a. Allogeneic and autologous cell components

We recommend that you, a sponsor, describe the following information in your IND:

- Cell Source: Tissue and cell type (e.g., colon, hematopoeitic, neuronal, T cells),
- Mobilization protocol: Whether or not donor cells are mobilized or activated in vivo in the donor,
- Collection method: The procedure used to obtain cells (e.g., surgery, leukapheresis (indicate device used if possible)) and the name and location of the collection facility, and
- Donor Screening: The donor safety testing that is performed. FDA has issued draft guidances on “Class II Special Controls Guidance Document: Human Dura Mater” (Ref. 4), “Draft Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” (Ref. 5) and "Draft Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" – (Ref. 6), and final rule entitled Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps (Ref. 7). We recommend that you use these references (including the draft guidances, when

finalized) to assess whether, for donors of neural cells and tissue, the donor qualification criteria described in your IND are consistent with regulatory requirements.

1) Autologous

We recommend that you document whether the donor is positive for specific pathogens (e.g., human immunodeficiency virus (HIV), cytomegalovirus (CMV)) and assess whether the tissue culture methods used during the manufacture of the product could propagate the pathogen. Also, if the donor is positive for specific pathogens, or is not screened, describe precautions to prevent the spread of viruses or other adventitious agents to persons other than the autologous recipient.

2) Allogeneic

We recommend that you describe the donor testing performed for adventitious agents, such as: HIV-1, HIV-2, hepatitis B virus (HBV, surface and core antigen), hepatitis C virus (HCV), human T-lymphotropic virus types 1 and 2 (HTLV-1, HTLV-2), CMV, and others, as appropriate. (Ref. 6, 7). In addition, advise whether FDA-licensed, cleared, or approved test kits are used in these detection assays. Include a description of the type of serological, diagnostic and clinical history data obtained from the donor. Consider other issues such as typing for polymorphisms and major histocompatability complex (MHC) matching, where appropriate. If cord blood or other maternally derived tissue is used, describe testing performed on donor mothers.

<u>CMC Reviewers</u>: Communicate with the clinical reviewer on any issues or concerns relating to the clinical history or testing of the donor cells.

b. Cell Bank System

We recommend that you, a sponsor, describe the pertinent information, as described below, relating to the cell bank system (i.e., master cell bank (MCB), working cell bank (WCB), master viral bank (MVB), and working viral bank (WVB)) used in product manufacture. In addition, include a description of cell lines such as packaging cells, producer cells (bacterial or mammalian), and feeder cells. We further recommend that you describe the history, source, derivation, and characterization of each cell and viral bank, and the frequency at which testing is performed. For further information refer to the document "Points to Consider in the

Characterization of Cell Lines Used to Produce Biologicals" (Ref. 8). See also ICH document Q5D, "Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" (Ref. 9).

CMC Reviewers: Document and assess the testing that is performed on each cell bank. Determine if the most relevant and critical testing for the particular cellular product has been performed.

1) Master Cell Bank (MCB)/Packaging Cell Line [2, 3]

We recommend that you, a sponsor, submit to the IND information regarding MCB characterization, including testing to adequately establish the safety, identity, purity, and stability of the cells. This section will likely address:

- Product microbiologic characteristics: including sterility, mycoplasma, in vivo, and in vitro testing for adventitious viral agents, and replication competent virus (RCV), as appropriate (see section III below).
- Freedom from the presence of specific pathogens: including, for human cells, testing for CMV, HIV-1 & 2, HTLV-1 & 2, EBV, HBV, and HCV, and B19 (human Parvovirus) as appropriate. For cell lines that are exposed to bovine or porcine components (e.g., serum, serum components, trypsin), appropriate testing would include testing for bovine and/or porcine adventitious agents.
- Identity of the cells (and vector if applicable): including tests to distinguish the specified cells through physical or chemical characteristics of the cell line (i.e., phenotype, genotype, DNA sequence, or other markers). For bacterial cell banks, include testing for strain identity, selection resistance; and consider testing for bacteriophage.
- Purity of bank cells, including identification and quantification of any contaminating cells.
- Activity of cells (e.g., activated lymphocytes, dopamine secretion, insulin secretion) and cell maturation (e.g., dendritic cells).

[2] If an ecotropic cell line was used during the generation of a retroviral producer cell line, we recommend that sponsors test for ecotropic retrovirus (see "Product testing"). Reviewers would assess and document the testing that was performed.

[3] If a feeder cell line of animal origin is used to propagate human cells (i.e., human and non-human animal cells are co-cultivated) the final product falls within the definition of xenotransplantation product. Refer to the "Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans" (Ref. 10) and "PHS Guideline on Infectious Disease Issues in Xenotransplantation." (Ref. 11)

- Processes critical to product safety, including:

    - Culture conditions used, including documentation of all media and reagents/components used during production, with copies of relevant certificates of analysis (COA),
    - Method of introduction of vector (transfection, transduction, infection) into MCB/parental cells to establish vector producer cell,
    - Analysis and selection of producer cell clone,
    - Cryopreservation, storage, and recovery of the MCB, including information pertaining to cell density, number of vials frozen, storage temperature, and cell bank location, and Genetic and phenotypic stability of the MCB after multiple passages, as well as viability of cells after cryopreservation. FDA recommends that, while the IND is in effect, you perform a stability assessment on the end of production cells (EOP) as a one-time test. This testing is usually performed later in product development and is required as part of the license application.

2) Master Viral Bank (MVB)

We recommend that you, a sponsor, provide a description of the MVB and the testing that you have performed to assure safety, purity, and identity. We recommend that you address:

- History and derivation of the MVB,
- Culture conditions used during tissue culture scale up,
- Testing of media and other reagents used during production, including COAs,
- Product microbiologic characterization – including sterility, mycoplasma, in vivo and in vitro testing for adventitious viral agents,
- Freedom from the presence of specific pathogens, such as human viruses if the cell line is of human origin, or pathogens specific to the origin of the production cell line (e.g., murine, non-human primate, see MCB above),
- Tests to identify presence of replication competent virus,
- Identity testing to establish the presence of gene therapy vector and therapeutic transgene (e.g., Southern blot), and
- Information pertaining to the cryopreservation of the MVB, including condition and storage location(s).

3) Working Cell Bank (WCB)/Working Viral Bank (WVB)

The WCB/WVB may have been derived from one or more vials of the MCB/MVB. As discussed in the guidance documents referenced above, the amount of information needed to document characterization of the WCB/WVB is usually less extensive than that needed to document characterization of the MCB/MVB. If there is a two tiered cell bank system in place, we recommend that you test the WCB/WVB for:

- In vitro adventitious viral agent testing,
- Replication competent virus,
- Bacterial and fungal sterility,
- Mycoplasma, and
- Limited identity testing (e.g., Southern blot).

3. Reagents

Under this section, we recommend that you, a sponsor, list any reagents used in manufacturing the product. For the purpose of this guidance, reagents are those components that are essential for cellular growth, differentiation, selection, purification, or other critical manufacturing steps but are not intended to be part of the final product. Examples include fetal bovine serum, trypsin, growth factors, cytokines, monoclonal antibodies, antibiotics, cell separation devices, and media and media components. These reagents can affect the safety, potency, and purity of the final product, especially by introducing adventitious agents.

a. Tabulation of Reagents Used in Manufacture

We recommend that you, a sponsor, list in your IND all reagents used during product manufacturing, including those added to culture media, and that you provide the following information for each reagent:

- Concentration of the component at the manufacturing step at which it is used,
- Vendor/supplier,
- Source: If a component is human derived, the procedures that are in place to assure that no recalled lots were used during manufacture or preparation of the product. If porcine products are used, a COA or other documentation that the products are free of porcine parvovirus. If a component is derived from a ruminant animal, the country of origin and whether bovine spongiform encephalopathy (BSE) or a substantial risk for BSE exists in the

country of origin. For more information refer to http://www.fda.gov/cber/BSE/BSE.htm.

CMC Reviewers: For all animal derived products, enter the following information in the animal components database: source organism, supplier/vendor, country of origin, and stage of manufacture. Additionally, notify the clinical reviewer if there are materials that are derived from ruminant animals.

- Reagent quality: We recommend that you, a sponsor, use FDA-approved or clinical grade reagents whenever they are available.

  CMC Reviewers: If the reagent is regulated as a drug or device, consider whether a consultative review should be obtained. See section II.4 below for further information about consultative reviews. Refer to the guidance on "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" (Ref. 12) for examples of expected information.

- COA or cross-reference letters: If you, a sponsor, are using a research grade (not FDA approved) reagent as part of the manufacturing process, we recommend that you provide information verifying the source, safety, and performance of the reagent. If the vendor of the reagent has a regulatory file with the FDA, a cross-reference letter from the sponsor may be provided in the IND. If a COA from the reagent manufacturer is used, you may assess whether the testing performed is adequate (see "Qualification Program" below) and provide that information in the IND.

  CMC Reviewers: For letters of cross-reference, include the regulatory file number and consider the need for a consultative review to determine whether there are any safety or other outstanding issues.

b. Qualification Program

If the reagent is not FDA approved, additional testing may be needed to ensure the safety and quality of the reagent. We recommend that you establish a qualification program that includes safety testing (sterility, endotoxin, mycoplasma, and adventitious agents), functional analysis, purity testing, and assays to demonstrate the absence of potentially

harmful substances (e.g., residual solvent testing). FDA believes that the appropriate extent of testing will depend on how the specific reagent is used in the manufacturing process.

c. Determination of Removal of Reagents From Final Product

We recommend that you test the final product for residual manufacturing reagents with known or potential toxicities and that you describe the test procedures you use to detect residual levels of these reagents in the final product. We recommend that you determine whether a qualification study is sufficient to document their removal, or whether lot release testing is appropriate prior to initiation of clinical trials.

d. Other Concerns

Because some patients may be sensitive to penicillin, we recommend that you, a sponsor, do not use beta-lactam antibiotics during the manufacturing of a therapeutic product for humans. If beta-lactam antibiotics are used, we recommend that you take and describe precautions to prevent hypersensitivity reactions.

CMC Reviewers: If beta lactam antibiotics are used during manufacture, consult with the clinical reviewer concerning appropriate exclusion criteria for the study and proper informed consent to address potential patient sensitivity. Discuss with the sponsor whether antibiotics can be eliminated or alternative antibiotics should be considered.

4. Additonal Considerations

a. Combination Products

This guidance applies to combination products that are assigned to CBER as the lead Center, and contain a human gene therapy biological product in combination with a drug or device as part of the final product.[4] The drug or device component may already have an FDA marketing approval (e.g., a new drug application (NDA), a premarket approval application (PMA), or a 510(k)), or it may be investigational.

CMC Reviewers: Determine the regulatory status of the drug or device either by contacting the RPM or the sponsor directly, if necessary. If the

[4] Regulations on combination products are found in 21 CFR Part 3, which describes how the agency will determine which component of FDA has primary jurisdiction for the premarket review and regulation of a combination product. CMC Reviewers: If you have any concerns regarding the appropriateness of the jurisdictional assignment or regulatory mechanism, you should contact the Office of Cellular, Tissues, and Gene Therapies jurisdictional officer.

drug or device has been approved for any use, confirm and document this in your review. You should request a consultative or collaborative review from the Center for Drug Evaluation and Research (CDER) or Center for Devices and Radiological Health (CDRH), in most cases, even if the drug or device component was previously approved for another use. Confer with your supervisor if it is unclear whether a consultative or collaborative review is needed.

If information describing the drug or device component has already been submitted to FDA (for example in another IND, IDE, or Master File), you, a sponsor, may submit a letter of cross-reference authorizing FDA to examine that previous submission for CMC or other information related to the drug or device component of your product.

CMC Reviewers: Document the submission of an adequate letter of cross-reference and verify that the cross-referenced file contains the needed information. Inform the consultative or collaborative reviewer that the information referenced in the letter of cross-reference is available to assist with the review.

b. Consultative Reviews

CMC Reviewers: Follow the standard operating procedures and policies (SOPP) on the "Intercenter Consultative/Collaborative Review Process" (Ref. 14). Specify the questions the consultative reviewer should address, identify the specific sections of the IND applicable to those questions, and request a date for completion of the consultative review. The requested date should be determined by coordinating with the consulting review center, and be based on timeframes mandated by statute, the priority of the consultative review request, and the workload of the designated reviewer. The RPM will request the consultative or collaborative review from the appropriate Center/Division using the form in Appendix 1 of the SOPP. Given the tight IND deadlines, you should work with the RPM to contact the appropriate Center/Division before sending the consultative request to identify the appropriate reviewer and ensure that the review can be completed within the time requirements. Also, as described in the SOPP, the RPM should send the Office of Combination Products a copy of the consultative/collaborative request for monitoring/tracking purposes. You should follow up with the consultative reviewer to confirm that essential documents are received along with the consultative review request. If problems that affect the timeliness of the consultative review occur during the consultative review period, discuss with your supervisor how to share these experiences with the Office of Combination Products, which is responsible for monitoring the efficiency and effectiveness of the intercenter consultative/collaborative review process.

i. Review of Device Component

CMC Reviewers: In the device consultative/collaborative review request, describe the device component, and where to find relevant information in the submission. Ask the consultative reviewer to identify concerns with how the device will be used, to determine whether appropriate biocompatibility and other device testing were performed adequately, and to assess testing of any hardware and software controlling the hardware. In addition, if the sponsor asserts barrier or performance claims, identify information for the consultative reviewer to assess relative to these claims. Document in the review basic information concerning the device, such as the device name, vendor or source, purpose, regulatory status, and a brief description of the device. When the consultative review is completed, attach it to your review and communicate any outstanding issues to the sponsor

ii. Review of Drug Components

CMC Reviewers: In the drug consultative/collaborative review request, describe the drug component of the combination product and state where to find relevant information on the component in the submission. Ask the consultative reviewer to identify any concerns with how the drug will be used and also to evaluate the methods of manufacturing and the adequacy of results from testing of the drug substance and/or drug product. Document in your review basic information concerning the drug component, such as the drug name, vendor or source, purpose, regulatory status, and a brief description of the use of the drug. When the consultative review is completed, attach it to your review and communicate any outstanding issues to the sponsor, as appropriate.

c. Summarize any Areas of Concern to be Addressed

CMC Reviewers: Summarize any areas of concern identified during the review of the product components. Discuss these concerns with the sponsor and/or communicate them in a letter to the sponsor, as described in section X below.

B. Product Manufacturing - Procedures

We recommend that you, a sponsor, include a detailed description of all procedures used during the collection, production and purification of a gene therapy product. We believe that a schematic of the production and purification process, and in-process and final product testing, helps to provide this information more clearly.

CMC Reviewers: If provided by the sponsor, append a copy of the process schematic to the IND review. In addition, summarize any areas of concern identified during the review of the product manufacturing procedures. Discuss these concerns with the sponsor and/or communicate in a letter to the sponsor, as described in section X below.

1. Vector Production/Purification

We recommend that you, a sponsor, describe the procedures used during the generation of the gene therapy vector, including:

- Culturing procedures, and media components used, including serum, growth factors, and antibiotics used during cell propagation,
- Brief description of cell passage number and cell plating density required during production of vector product, and
- All purification steps in order of processing, for example: centrifugation, column purification, and density gradients.

2. Preparation of ex Vivo Gene-Modified Autologous or Allogeneic Cells

Autologous or allogeneic cells can be modified by using viral or plasmid vectors. We recommend that you, a sponsor, describe the following procedures:

a. Method of Cell Collection/Processing/Culture Conditions

We recommend that you describe the volume and number of cells collected. Include any mechanical or enzymatic digestion steps used, and describe the use of any cell selection device or separation device, including density gradients, magnetic beads, or fluorescence activated cell sorting (FACS). Include a description of culture systems (flasks, bags, etc.), and state whether the system is closed or open. Describe any in-process testing that will be performed during these procedures.

b. Ex Vivo gene modification

We recommend that you describe in detail the modification procedure, such as transduction, transfection, or infection. Describe in detail the selection of cells (methods, devices, reagents) as well as any other cell modification steps such as irradiation. If the cells are cultured after the genetic modification occurs, include the culture conditions used and time in culture.

c. Irradiation

We recommend that, if the autologous or allogeneic cell product is irradiated before injection, you provide data to demonstrate that the cells are rendered replication incompetent, but still maintain their desired characteristics after irradiation. Describe the documentation of calibration of the cell irradiator source.

d. Process Timing & Intermediate Storage

We recommend that you report the approximate time elapsed for each step from cell collection to final harvest. It is important to know the time limit of each step in production to determine what, if any, in-process testing to perform. If cells are cryopreserved before injection into patients, include this information along with any stability studies initiated (see section V.A.1 below). Describe the time and conditions of storage between cell collection and final harvest.

CMC Reviewers: Describe and assess the procedures in place to ensure the stability of the bulk harvest while in storage.

3. Final Harvest

We recommend that you, a sponsor, provide a detailed description of the final harvest. Advise whether the final cell harvest is centrifuged prior to final formulation, and if so, describe the wash conditions and media used. Advise whether the cells are cryopreserved after formulation or formulated immediately and given to the patient. If the final harvest is stored, describe the storage conditions and the length of storage.

4. Final Formulation

You must describe the formulation of the final product, (21 CFR 312.23(a)(7)(iv)(a)). We recommend that you describe whether any excipients such as growth factors, or human serum albumin are included in the final formulation and state their source (see section II.A.3 above). Identify the vendor and final concentration of these excipients. Describe the cell density or concentration or vector concentration used in the final product. If the final product is delivered to the clinical site frozen, we recommend that you include a description of how the product will be shipped and data to show that the product can be thawed with consistent results.

IV. PRODUCT TESTING

If the manufacturing process is not controlled, it will be difficult to produce consistent products from lot to lot. This would make it difficult to identify the critical parameters necessary for the desired clinical effect. Refer to "FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products" (Ref. 14) for additional information.

Accordingly, FDA believes that appropriate product testing for gene therapy products includes, but is not limited to, microbiological testing (including sterility, mycoplasma, and adventitious viral agents) to assure safety, and assessments of other product characteristics such as identity, purity (including endotoxin), viability (for ex vivo gene modified products), and potency. FDA recommends that you, a sponsor, perform this testing throughout the manufacturing process, including the manufacture of cell and viral banks, to evaluate the manufacturing process itself and to ensure the quality and consistency of the product. We further recommend that you describe the specifications used for intermediate acceptance criteria and final product release criteria. Specifications are the quality standards (i.e., tests, analytical procedures, and acceptance criteria) that confirm the quality of products and other materials used in the production of a product. Acceptance criteria mean numerical limits, ranges, or other criteria for the tests described. Specifications should be appropriate to the stage of product development, because release criteria are generally refined and tightened as product development progresses toward licensure (see Appendix B). We recommend that you submit test results related to lot release, characterization testing, working cell banks, master viral banks, and working viral banks in tabular form including the lot number or identifier, date of manufacture, test, test method, the sensitivity and specificity of test methods when appropriate, release criteria, and test results**.**

CMC Reviewers: Document the testing performed. Assess the appropriateness of that testing and the acceptance criteria, based on any results previously obtained by the sponsor.

A. Microbiological Testing

We recommend that you, a sponsor, perform microbiological testing on cell banks, viral banks, in-process intermediates, and the final product, as appropriate.

1. Sterility Testing (Bacterial and Fungal Testing)

Current practices for sterility testing.

a. Test Method

Suitable sterility tests may include the test described in 21 CFR 610.12 and the test described in United States Pharmacopoeia (USP) <71> Sterility Testing (Ref. 15). If you are using another test method, we recommend that you describe its suitability. Note that under 21 CFR 610.9, prior to product licensing an alternative method must be shown to be equivalent to or better than these prescribed methods.

If you use antibiotics in manufacturing, we recommend that you provide documentation that the antibiotics were removed prior to sterility testing. If the antibiotics cannot be removed, we recommend that you assess the validity of the sterility assay using the bacteriostasis and fungistasis testing as described in USP <71> Sterility Tests (Ref. 15). Use of this assay is designed to ensure that any residual antibiotic present in the product does not interfere with the results of sterility testing.

CMC Reviewers: If an alternative to the acceptable sterility methods is being used, assess the adequacy of this alternative test method and either confirm that it has been validated to be equivalent to the testing prescribed in 21 CFR 610.12, or inform the sponsor that such validation will be required under 21 CFR 610.9 prior to product licensing.

b. Test Timing

Sponsors frequently perform in-process sterility testing at critical points during manufacturing, such as during extended culture periods, or after cells have undergone activation or other modification. We recommend that you, a sponsor, identify when in-process sterility testing is performed during manufacturing and the test method used. The test method used for in-process testing is at your discretion.

If you freeze the final product before its use, we recommend that you perform testing on the product prior to cryopreservation, so that results will be available before the product is administered to a patient. However, if the product undergoes manipulation (e.g., washing, culturing) after thawing, particularly if procedures are performed in an open system, you may need to repeat sterility testing. We recommend that you incorporate the results of in-process sterility testing into your acceptance criteria for final product specifications.

If you cannot complete 14 day sterility testing (21 CFR 610.12 or USP) because the final product must be administered before you obtain the results, we recommend that you perform a gram stain on the final formulated product and that you perform the full 14 day sterility testing on the final product and release the product based on a negative gram stain. If the final product is a genetically modified cellular therapy, and you can not complete 14 day sterility testing prior to administration, then we recommend that a sample of cells be taken 48-72 hours prior to final harvest or after the last re-feeding of the culture, and that you review the results of those sterility tests before you release the product. You would then use a no-growth result from the 48-72 hour sterility test and the negative gram stain for release criteria. We further recommend that you

perform the full 14 day sterility test, even after the product has been given to the patients. In all cases where product release is prior to obtaining results from a full 14 day sterility test, we recommend that you develop procedures describing actions to be taken in the event that the 14 day sterility test shows that the patient received a non-sterile product. FDA believes that such an event would be a serious and unexpected adverse experience, requiring notification to FDA and all participating investigators in accordance with 21 CFR 312.32(c) (1).

2. Mycoplasma

There are several potential sources of mycoplasma contamination. Two major sources include animal serum products used in culture, and the culture facility environment, particularly with open culture systems. FDA recommends that you, a sponsor, perform mycoplasma testing on the product at the manufacturing stage when the test is most likely to detect contamination, such as after pooling of cultures for harvest but prior to cell washing. Testing should be conducted on both cells and supernatant. FDA recommends that you advise whether there is in-process testing for mycoplasma during extended culture procedures. Due to the limited shelf life of many cellular products, it is frequently not feasible for a sponsor to perform the recommended culture-based assay (Ref. 8) for release testing. In those cases, we recommend the use of polymerase (PCR)-based mycoplasma assays or another rapid detection assay during product development. As part of your product licensing application, you would submit appropriate data to demonstrate that the alternative test has adequate sensitivity and specificity.

3. Adventitious Agent Testing

We recommend that, as appropriate, you, a sponsor, perform and describe in your IND adventitious agent testing as set out below. For more information on adventitious agent testing, refer to ICH guidance Q5A: "Guidance on Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin" (Ref. 16 and Ref. 8).

a. In Vitro Viral Testing

When cell lines are used, FDA recommends that you describe the cell lines and perform in vitro viral testing. In vitro viral testing should be performed on the MCB, WCB, MVB, WVB, end of production cells (EOP) and vector product. Testing should be conducted by inoculating the test sample (MCB, MVB, etc.) onto various susceptible indicator cell lines such as the human cell line MRC-5 or Vero cells which are primate in origin. The choice of cells used would depend on the species of origin of the product to be tested. An appropriate test would include monolayer

cultures of the same species and tissue as that used for production of the product, as well as a human and/or non-human primate cell line susceptible to human viruses. In addition, the test would include a measure of both cytopathic and hemadsorbing viruses.

b. In Vivo Viral Testing

When cell lines are used, FDA recommends that you perform and submit data on in vivo viral assays carried out by inoculating the test sample (MCB, MVB etc.) into animals such as adult and suckling mice, and embryonated hen eggs. Consider whether to include additional testing of guinea pigs, rabbits, or monkeys. Such studies would assess the test animals for any indication of illness. If such additional testing is appropriate, describe and explain the suitability of the animals used.

c. Selected Species-Specific Testing for Adventitious Viruses

FDA recommends that you test your MCB and MVB for appropriate, species-specific viruses. As described below, we recommend that you describe the testing that is performed, the different stages of manufacturing where those tests are performed (e.g., cell banks, viral banks, final product), and the test methods used.

1) Species-Specific Viruses

We recommend that you describe all species-specific virus testing performed on the MCB and MVB. We believe that all rodent cell lines used during product manufacturing should be tested for rodent specific viruses. These viruses are usually detected by antibody production tests, murine antibody production (MAP), rat antibody production (RAP), or hamster antibody production (HAP). If human cell lines are used in the therapeutic product, we recommend that you perform testing for human pathogens (CMV, HIV-1 & 2, HTLV 1 & 2, EBV, HBV, HCV, and B19, and other human viral agents, as appropriate. Human viral agents may be tested using a PCR-based test system.

FDA believes that when the gene therapy product is produced in a human cell line, e.g., an adenoviral vector produced in human 293 cells, you should test for the presence of additional human viruses such as adenovirus and adeno-associated virus (AAV), and describe those tests in your IND.

2) Testing for Retroviruses

FDA believes that when the MCB and MVB are used for production of vectors other than retroviral vectors, you should test the MCB and MVB for retroviral contamination using Reverse Transcriptase (RT) assays and electron microscopic analysis, and include a description of those tests in your IND.

We recommend that you perform testing for replication competent retrovirus (RCR) in the production of retroviral vectors at multiple points in production, including MVB, WVB, vector supernatants, end of production cells, and ex vivo modified cells. For further information on retroviral testing refer to the "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" (Ref. 17).

For cells that produce vectors containing amphotropic murine leukemia virus envelope, we recommend that you test for RCR using a permissive cell line such as *Mus dunni* and describe that testing in the IND. If an ecotropic packaging cell line is utilized during retroviral vector production, we recommend that you conduct and describe an ecotropic retroviral assay for the detection of low-level viral contamination in the MCB. Murine ecotropic viral contamination can be detected using either XC or D56 plaque assay methods.

We recommend that you describe how vector supernatant is tested. An appropriate test of vector supernatant lots would be by amplification on a permissive cell line such as *Mus dunni*, followed by detection in an appropriate indicator cell assay such as PG-4 S+L-. An appropriate test of the pooled End of Production (EOP) cells would be by co-culture with a permissive cell line such as *Mus dunni* for amphotropic virus, and the amplified material assayed in an appropriate indicator cell assay. In the case of ex vivo gene modified cells, if cells are cultured for ≥ 4 days, RCR testing would be appropriate. If ex vivo gene modified cells are cultured for < 4 days, archiving cells would be appropriate in place of active RCR testing. If it is not possible to have results from the RCR assay prior to treatment, we recommend that you initiate the culture assay and perform an alternative method (such as PCR) for product release.

3) Adenoviruses

For studies using adenoviral vectors, we recommend that you conduct tests for replication competent adenovirus (RCA) on MVB as well as the final vector. We believe that an appropriate maximum level of RCA contamination would be < 1 in 3 x 10^{10} viral particles, and that the adenoviral particle to infectious unit (iu) ratio would be ≤ 30 to 1.

B. Identity

We recommend that you, a sponsor, verify the identity of the MCB and the final product by assays that will identify the product and distinguish it from other products being processed in the same facility. For the final product, identity testing is important to ensure that the contents of the vial are labeled appropriately. For additional information on labeling, refer to section VI. B below.

If the final product consists of one or more cell lines, we recommend that you establish identity tests and/or controls that distinguish between the multiple cell lines used, and describe those tests and/or controls. Tests may include assays for cell surface markers or genetic polymorphisms (see Ref. 1 for additional information).

C. Purity

Product purity can be defined as freedom from extraneous material, except that which is unavoidable in the manufacturing process (21 CFR 610.13). Purity testing includes assays for pyrogenicity/endotoxin (see below), residual proteins or peptides used to stimulate or pulse cells, reagents/components used during manufacture, such as cytokines, growth factors, antibodies, and serum, and unintended cellular phenotypes.

1. Residual Contaminants

We believe that appropriate purity testing would include assays for residual peptides, proteins, DNA, RNA, solvents used during production and purification, and reagents used during manufacture such as cytokines, growth factors, antibodies, and serum. If the product is a gene therapy modified ex vivo cell product, we believe that appropriate purity testing would include a measurement of contaminating cell types or cell debris. For further information, refer to ICH Q3 on “Impurities” (Ref. 18). We recommend that you, a sponsor, describe in your IND the purity testing you conduct, and your specifications for release.

2 Pyrogenicity/Endotoxin

Endotoxin testing using the Limulus Amebocyte Lysate (LAL) assay method is typically done to detect pyrogens (endotoxin) for products in early-phase clinical trials, and for marketed products. If you are using the LAL endotoxin method, the process for manufacture may also need to be evaluated for production of intrinsic pyrogenic substances other than endotoxin using the pyrogenicity test described in 21 CFR 610.13 (b). For any parenteral drug, except those administered intrathecally, our guidance recommends that the upper limit for endotoxin be 5 EU/kg body weight/dose. For intrathecally administered drugs, we recommend a lower limit of 0.2 EU/kg body weight/dose. However, specifications should be based on your available data. For further information, refer to the guideline on "Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices" (Ref. 19). We recommend that you, a sponsor, describe in your IND the pyrogenicity/endotoxin testing you conduct, and your specifications for release.

CMC reviewers: Document in your review the specification for endotoxin testing and verify that testing is on the final product and that results are available prior to lot release.

D. Potency

We recommend that you, a sponsor, describe and justify all assays you will use to measure potency. We recommend that these assays be quantitative, but in addition they may include a qualitative biological assay. For a Phase 1/Phase 2 study, we recommend that the assay quantify the expression of a gene therapy vector product. For a Phase 3 study, we recommend that the potency assay consist of in vivo or in vitro tests that measure an appropriate biological activity. Note that potency assays should be validated prior to licensure.

E. Other

1. General Safety

Testing for general safety is required for licensure of all gene therapy vector products, unless the product is exempt under 21 CFR 610.11(g). General safety testing is performed on biological products intended for administration to humans and specific tests are described in 21 CFR 610.11. We recommend that you inform FDA whether general safety testing is being performed during product development.

CMC reviewers: Advise the sponsor regarding the applicability of the general safety test for the product under review. (Ref. 20)

2. Viability

If your product includes cells, we recommend that you, a sponsor, establish minimum release criteria for viability. For genetically modified somatic cellular therapies, the minimum acceptable viability specification is generally set at 70 percent. If this level cannot be achieved, we recommend that you submit data in support of a lower viability specification, demonstrating that dead cells and cell debris do not affect the safe administration of the product, and/or its therapeutic effect. For further information, see Ref. 1.

3. Cell Number/Dose

We recommend that you develop specifications for the minimum number of viable and functional cells as part of product testing and release. We recommend that you advise whether a maximum number/dose of cells to be administered has been established, and the basis for that level. For administration of a gene vector, describe your dose as the concentration of plasmid DNA, viral particle number, or titer.

V. FINAL PRODUCT RELEASE CRITERIA TESTING

The final product is the final formulated product used for patient administration. In the case of a gene therapy product, this would include, for example, the vialed vector or ex vivo genetically modified cells. Final product release criteria testing should be performed on each lot of product manufactured. In some situations, each dose could be considered a single lot, depending on the manufacturing process. The results from final product release criteria testing should be available prior to administration to a patient. If results from final product testing will not be available prior to release, we recommend that you, a sponsor, clearly indicate this in the IND, together with your specifications, and include a description of the reporting notification process if the acceptance criteria are not met. We recommend that you provide, in table format, all of your proposed specifications (tests for safety, purity, potency, and identity as described in Section III, test methods, and acceptance criteria), including test sensitivity and specificity, where appropriate, for the final product. (Note that, before the product may be licensed, these parameters should be validated. (21 CFR 211.165(e))

VI. PRODUCT STABILITY

Stability testing is performed during early phases of the clinical trial to establish that the product is sufficiently stable for the time period required by the study (21 CFR 312.23(a)(7)(ii)). Data supporting a final formulation and dating period will be necessary for licensure. We recommend that you, a sponsor, describe the stability measures you will use to support your studies. For further information, refer to ICH Q5C: "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products," (Ref. 21), ICH Guideline Q1A(R): "Stability Testing of New Drugs and Products" (revised guideline) (Ref. 22), ICH Guideline Q1E: "Evaluation of

Stability Data" (Ref. 23), and when finalized, the draft guidance on "Stability Testing of Drug Substances and Drug Products" (Ref. 24).

CMC Reviewers: Assess the product development plan in the IND review to determine how much stability data is needed for the current phase of investigation and whether or not sufficient data is included in the submission. If submitted, include preliminary data in your review. Assess whether proposed expiration dating is appropriate.

A. Stability Testing

As stated in 21 CFR 312.23 (a)(7)(ii), you, a sponsor, must conduct stability testing in all phases of the IND, to demonstrate that the product is within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation. If a very short term clinical investigation is proposed, the stability data submitted may be correspondingly limited. We recommend that you submit a stability protocol and data for both in-process material and the final gene therapy product. We believe that a proposed stability protocol should include a measure of product sterility, identity, purity, quality, and potency. For each test conducted, describe the test method, sampling time points (there should be a zero-time point), testing temperature, and other appropriate information, including your justification of the assays used to indicate product stability, measuring these parameters for the duration of storage required by the clinical protocol.

CMC Reviewers: If the sponsor plans to use the product past the duration of the clinical trial (e.g., for a separate trial being conducted after the initial trial), verify that testing establishes stability throughout the relevant time period.

1. In-process stability testing

If cells are cryopreserved, we recommend that you describe the stability protocol used to ensure that the product is stable during the period of cryopreservation, measuring the parameters described above, as appropriate. A comparison is often made of analyses carried out pre-freeze and post-thaw. Describe any stability testing performed on the product during the holding steps, such as cryopreservation of cells, holds between vector harvests, and storage of bulk product.

2. Final product stability testing

We recommend that you include any data that demonstrate that the product is stable between the time of product formulation and patient infusion to aid in establishing an expiration-dating period. We recommend that you conduct the testing at the appropriate temperatures and at time points consistent with predicted storage times. If the product is shipped from the manufacturing site to the clinical site, describe the time and shipping conditions (i.e., packaging, temperature). We believe that your stability protocol should be adequate to demonstrate that product

integrity, sterility, and potency are maintained under the proposed shipping conditions. We further recommend that validation studies using conditions that stress the system be initiated by Phase 3 and completed prior to submission of a biologics license application.

VII. OTHER ISSUES

A. Product Tracking

For autologous or patient-specific products, we recommend that you, a sponsor, establish a product tracking and segregation system. An adequate system would track the therapeutic product from collection to administration of the product and would include procedures to ensure that the product is segregated from other products in incubators, hoods, and cryopreservation units.

B. Labeling

If more than one site is involved in the study, we recommend that you describe the product labeling used throughout the manufacturing process, and the labeling that you use to ensure that a product will reach the proper clinical site. We recommend that the product label contain the date of product manufacture, storage conditions, expiration date and time (if appropriate), product name, and two patient identifiers. As described in 21 CFR 312.6(a), the label for an investigational product must contain the following statement "Caution: New Drug – Limited by Federal Law to Investigational Use". For both autologous and allogeneic therapies, if the subject was neither screened nor tested for adventitious agents, or if no testing was performed on the cellular product, labeling may carry the warning "Not Evaluated for Infectious Substances." "Warning." For more information, refer to Ref.6.

C. Container/Closure

We recommend that you describe the types of container and closure used, and that you determine that the containers and closures are compatible with the product. For more information, see Ref. 25.

D. Environmental Impact

Under 21 CFR 312.23(a)(7)(iv)(*e*), you must submit either a claim for categorical exclusion under 21 CFR 25.30 or 25.31, or an environmental assessment under 21 CFR 25.40. Such categorical exclusion is ordinarily granted, absent extraordinary circumstances indicating that the specific proposed action may significantly affect the quality of the human environment. Extraordinary circumstances are described in 40 CFR 1508.27 and may include actions that create a potential for serious harm to the environment and actions that adversely affect a species or the critical habitat of a species determined to be endangered, threatened, or entitled to special protection (21 CFR 25.21).

See the "Guidance for Industry: "Environmental Assessment of Human Drug and Biologics Applications" (Ref. 26) for additional information.

CMC Reviewers: Document in your review the sponsor's assessment of any extraordinary circumstances concerning this product.

E. Qualification of the Manufacturing Process

The manufacturing process for gene therapy products entails the use of reagents and source materials of differing complexity, variability and risk for introduction of adventitious agents. Qualification of reagents and source materials, as well as ensuring that appropriate controls are in place for monitoring manufacturing consistency and product quality, are key elements in ensuring that patients receive a safe, consistent, and potent product. We believe that, prior to production of clinical lots and initiation of clinical studies, procedures should be in place to ensure proper manufacturing oversight. This includes programs for quality control (QC), and the identity of responsible individuals and their duties.

We recommend that you describe the product manufacturing quality assurance (QA) and quality control (QC) programs in place to prevent, detect, and correct deficiencies that may compromise product integrity or function, or that may lead to the possible transmission of adventitious infectious agents. Identify each individual who has authority over QA and QC programs and list that individual's duties. Include the dates of the last QA and QC audits of your manufacturing operations and those of contract manufacturers, vendors or other partners.

We further recommend that you describe the changeover procedures that are followed to ensure that no cross-contamination occurs between different gene therapy vectors, or among an individual patient's cells and other products stored or produced in the same facility. Describe the use of PCR assays for detecting cross-contaminating vector sequences, area clearance, cleaning and decontamination reagents, and segregation of activities and the qualification of aseptic processing steps. Because most gene therapy products are not subject to final sterile filtration prior to patient infusion, we believe that these products should be manufactured under aseptic conditions. A media fill is an appropriate method of assuring that the process consistently produces a sterile product. Refer to the "Guideline on Sterile Drug Products Produced by Aseptic Processing" (Ref. 27) for further information. Prior to licensure, the facility and all processes used to manufacture the product must be validated, and all equipment used for manufacturing and testing must be qualified. (See, for example, 21 CFR 211.42, 211.46, 211.63, 211.100, 211.160, and 211.165)

CMC Reviewers: Obtain consultative reviews from the Division of Manufacturing and Product Quality to assess any data submitted by the sponsor on facilities and environmental issues such as decontamination and cleaning validation.

F. Biostatistics

CMC Reviewers: Obtain consultative reviews for relevant portions of the CMC section from the Division of Biostatistics to ensure the adequacy of proposed experimental designs and analytic plans. There are many significant design and analysis issues in the areas of assay validation, establishing specifications, evaluation of product potency, and evaluation of product stability. Proper statistical design and analysis of such studies are essential to assure reliable documentation of the safety, purity, and potency of the product. If applicable, document in your review recommendations from the Biostatistics consult.

VIII. PRECLINICAL STUDIES TO BE DOCUMENTED BY FDA CMC REVIEWERS

A. Summary of Concept Studies

CMC Reviewers: Document information provided by the sponsor to support the scientific rationale underlying the proposal. Include a brief summary of preclinical data that was generated using either in vivo animal studies or in vitro studies to assess the product's activity and efficacy. Some issues specific to gene therapy that should be documented include localization or trafficking of vectors, and level and persistence of gene expression.

B. Gonadal Distribution

CMC Reviewers: For gene therapy vectors used for direct in vivo administration, work in consultation with the pharmacology/toxicology reviewer to document data that demonstrate the extent to which a vector is able to disseminate out of the administration site and distribute to the gonads. In most cases, this information is not available at the beginning of the Phase 1 study but would become available in the course of product development. Such data are usually obtained by using a PCR assay. In cases where a novel vector, route of administration, indication, or vector delivery system is proposed, preclinical studies to assess vector dissemination may be appropriate prior to initiation of the Phase 1 study. Document in your review the sensitivity of this assay (amount vector/μg cellular DNA), including assay controls (positive, negative and spiked controls). We believe that the PCR assay sensitivity should be less than 100 copies of vector genome per μg cellular DNA.

IX. CLINICAL STUDIES TO BE DOCUMENTED BY FDA CMC REVIEWERS

CMC Reviewers: Provide a brief description of the following in the CMC review:

- Protocol title
- Patient Population
- Route of Administration
- Dose

Include the dosing regimen and whether there is a dose escalation. Document the dosing range and number of patients enrolled in each dose. Note whether the dose escalation is intra-patient or inter-patient and what time interval/data evaluations occur between dose increases.

A. Frequency

Include the frequency of dose injections per treatment cycle and the number of proposed cycles.

B. Genetic, Biochemical, and Immunological Testing

Assess, in conjunction with the clinical reviewer, whether all genetic and/or product-specific biochemical and immunological testing being done on the patient is appropriate and whether the test has been appropriately developed and validated for the stage of clinical investigation. Evaluate the sensitivity and specificity of the test methods used to demonstrate biological activity (e.g., immunological assay, PCR) and document this information in your review. In conjunction with the clinical reviewer, verify and document that serum from a patient on a retroviral gene therapy protocol is analyzed at 3, 6, and 12 months after treatment for the presence of RCR. If all post-treatment assays are negative during the first year, then yearly patient samples may be archived (see Ref. 17).

C. Informed consent

If the informed consent document is submitted for your review verify that the product is described accurately and completely.

D. RAC Review

If the sponsor or the sponsor's institution receives NIH funding for DNA recombinant studies or if any clinical sites used in the study receive NIH funding for Recombinant DNA studies, inform the sponsor that under the NIH Recombinant DNA Guidelines, NIH will not allow the protocol to be initiated until RAC review has occurred. Confirm that the sponsor has submitted the protocol to the Recombinant DNA Advisory Committee (RAC) for review. For additional information refer to the "NIH Guidelines for Research Involving Recombinant DNA Molecules" (see Ref. 28).

X. RECOMMENDATION TO BE DETERMINED BY FDA CMC REVIEWERS

CMC Reviewers: Describe any information that is missing or incomplete, and issues that require additional clarification. Provide an overall assessment, from the CMC perspective, of whether the trial may proceed or should be placed on clinical hold. Document all information obtained from the sponsor through telephone conversations or faxes. Note this documentation in the Recommendation Section of the Product Review Template, throughout the review document, or

as an attachment to the review, as appropriate. Upon completion, sign and date the review and then obtain concurrence from your supervisor.

XI. COMMENTS TO SPONSOR GENERATED BY FDA CMC REVIEWERS

CMC Reviewers: Draft comments on unresolved issues to be addressed either (1) before initiating clinical studies after an investigation has been placed on clinical hold or (2) as product development progresses (i.e., when there is no clinical hold) as discussed below. Refer to SOPP 8201, "Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications" (Ref. 29), for additional information. Forward your comments to the RPM for inclusion in a letter to the sponsor, after you have obtained supervisory concurrence on your review.

A. Clinical Hold

These are comments that the sponsor must satisfactorily address prior to allowing clinical studies to proceed after FDA has imposed a clinical hold. These comments must meet the criteria listed in 21 CFR 312.42(b).

B. Non-Clinical Hold

These are comments that the sponsor would address as product development progresses. In some cases a sponsor may need to address specific manufacturing issues by a certain point in clinical development, such as prior to initiation of Phase 3 studies. Your comments should inform the sponsor of any such issues.

XII. APPENDICES

XIII. APPENDIX A – PRODUCT REVIEW TEMPLATE

Product Review Template (Gene Therapy)

PRODUCT REVIEW (Gene Therapy)

Supervisor Concurrence/Date

IND:	XXXX	**Sponsor's Submission Date:**	Month DD, YYYY
		30 Day Review Date:	Month DD, YYYY
		STATUS:	Pending

DATE: Month DD, YYYY

REVIEWER: Your Name
Your Title, OCTGT/DCGT/Your Branch

THROUGH: Branch Chief Name
Branch Chief, OCTGT /DCGT/Branch

SPONSOR: Name:
Address:
Title:
Phone:
Fax:

SPONSOR POINT OF CONTACT:
Name:
Address:
Title:
Phone:
Fax:

TITLE OF IND:

PROPOSED USE:

REVIEW TEAM: Clinical:
Pharm-Tox:
RPM:
Consults:

PRODUCT DESCRIPTION:

PHASE OF STUDY:

CROSS-REFERENCED INDs, IDEs, MFs:

KEYWORDS:

INTRODUCTION / RATIONALE:

STUDY OBJECTIVES:

PRODUCT MANUFACTURING AND CHARACTERIZATION

PRODUCT MANUFACTURING - COMPONENTS

VECTOR

CELLS

Allogeneic or Autologous cell components

Cell Source:

Method of Collection:

Donor Screening:
Description

Tabulation of Testing

Cell Bank System -

Master Cell Bank (MCB)
Description

Tabulation of Testing

Working Cell Bank (WCB)
Description

Tabulation of Testing

Master Viral Bank (MVB)

Description

Tabulation of Testing

Working Viral Bank (WVB)
Description

Tabulation of Testing

Reagents

Tabulation of Reagents Used in Manufacture

Reagent/Excipient	Concentration at use	Source	Grade	Vendor	COA

Qualification Program

Determination of removal of reagents from final product

Combination Products - if applicable

Drug or Device Components - if applicable

Consult Review Issues

Areas of Concern for Components

Product Manufacturing - Procedures

Vector Production and Purification

Preparation of Ex Vivo Modified Cells

Method of cell collection/ processing/culture conditions

Ex Vivo Modification

Irradiation - if applicable

Process timing & intermediate storage

FINAL HARVEST

Timing/Methods/Wash procedure

FINAL FORMULATION

Formulation/infusion buffer

Excipients

Cell density/concentration in the final product

Storage method prior to use

Areas of Concern for Manufacturing

PRODUCT TESTING

IN-PROCESS TESTING AND CRITERIA

Tabulation of Tests, Manufacturing Step, Test Methods, Test Sensitivity & Specificity, and Criteria

Test	Manufacture Step Where Performed	Method	Specification	Sensitivity	Specificity

Description of Test Methods

FINAL PRODUCT RELEASE CRITERIA /SPECIFICATIONS

Tabulation of Final Product Release Criteria Tests, Test Methods, Specification, Test Sensitivity & Specificity

Test	Method	Specification	Sensitivity	Specificity	Results Available Prior to Release

Description of test method

Product Stability

IN-PROCESS STABILITY TESTING

Cryopreserved Cells:

Other intermediate holding steps

FINAL PRODUCT STABILITY TESTING

Product formulation to patient infusion

Shipping conditions

Other Issues

PRODUCT TRACKING

LABELING AND CONTAINERS

In-process Labeling

Final Product Labeling

CONTAINER CLOSURE & INTEGRITY

ENVIRONMENTAL IMPACT

VALIDATION AND QUALIFICATION OF THE MANUFACTURING PROCESS

QA/QC PROGRAM

Manufacturing Process Validation

Biostatistics

NOVEL ISSUES

Preclinical Studies

Clinical Studies

PROTOCOL TITLE

PATIENT POPULATION

ROUTE OF ADMINISTRATION

DOSE

FREQUENCY

GENETIC AND BIOCHEMICAL, AND IMMUNOLOGICAL TESTING

INFORMED CONSENT

Recommendation

COMMENTS TO SPONSOR

CLINICAL HOLD

NON-CLINICAL HOLD

Signature Date:_____
Reviewer Name

XIV. APPENDIX B - CONSIDERATIONS FOR DEVELOPMENT OF FINAL PRODUCT RELEASE CRITERIA SPECIFICATIONS AND STABILITY PROTOCOLS

- Specifications are the quality standards (i.e., tests, analytical procedures, and acceptance criteria) that confirm the quality of products and other materials used in the production of a product. Acceptance criteria are the numerical limits, ranges, or other criteria for the tests described. For additional information, see ICH Guideline Q6B: "Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" (Ref. 30). FDA believes that certain release specifications, such as those related to product safety, should be in place prior to initiating Phase I clinical studies. As product development proceeds, additional specifications for product quality and manufacturing consistency are developed and implemented. For additional discussion of manufacturing quality control, see "Guidance for Industry: Guideline on the Preparation of Investigational New Drug Products" (Ref. 31) and Guidance for Industry: "IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information" (Ref. 32).

A. Development of Release Acceptance Criteria

FDA recommends that proposed release acceptance criteria for the final product be based on scientific data and manufacturing experience obtained during development of the product as described below:

- Phase 1 - Based on data from lots used in preclinical studies.
- Phase 2 - Refine and tighten based on data generated during Phase 1.
- Phase 3 - Based on information collected during product development.
- Licensure - Based on information collected during product development using validated assays.

B. Development of Acceptance Criteria Analytical Procedures

FDA recommends that proposed analytical procedures be based on scientific data and manufacturing experience as described below:

- Phase 1-3 – Usually based on Code of Federal Regulation (CFR) methods or alternative methods, if appropriate.
- Phase 2 - If an alternative to the CFR method is used, FDA recommends that the sponsor initiate validation of the alternative method by Phase 3.
- Licensure – The product specification should be in place and established under a validated assay.

C. Development of Stability Protocols

In order to develop adequate stability data for timely submission in a license application, FDA recommends that a sponsor implement and expand the stability program as described below:

- Phases 1-3 – Preliminary data on product stability must indicate whether the product or components are likely to remain stable for the duration of the clinical trial. Note: the regulations require that the IND contain this data at each stage of the clinical trial. (21 CFR 312.23(a)(7)(ii)).
- Phase 2 – FDA recommends that the sponsor initiate a stability protocol to accumulate additional data.
- Phase 3 – FDA recommends that the sponsor begin to establish the dating period, storage conditions, and shipping conditions based on data derived from the stability protocol.

XV. APPENDIX C - RELEVANT REGULATORY DOCUMENTS

Most are available for downloading from: **http://www.fda.gov/cber/guidelines.htm**.

1. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy, dated March 1998, **http://www.fda.gov/cber/gdlns/somgene.pdf**

2. 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/cder/guidance/phase1.pdf**

3. Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs), dated August 2003, **http://www.fda.gov/cber/gdlns/cmcsomcell.pdf**

4. Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Human Dura Mater, dated December 18, 2003, **http://www.fda.gov/cdrh/ode/guidance/054.html**

5. Draft Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), dated June 2002, **http://www.fda.gov/cber/gdlns/cjdvcjd0602.htm**

6. Draft Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), dated May 2004 **http://www.fda.gov/cber/gdlns/tissdonor.pdf**

7. Final Rule: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue -Based Products, (69 FR 29786, May 25, 2004), **http://www.fda.gov/cber/rules/suitdonor.pdf**

8. Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (1993), July 12, 1993, **http://www.fda.gov/cber/gdlns/ptccell.pdf**

9. ICH Guidance on Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products, (63 FR 50244, September 21, 1998), **www.fda.gov/cber/gdlns/qualbiot.pdf**

10. Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans, dated April 2003, **http://www.fda.gov/cber/gdlns/clinxeno.pdf**

11. PHS Guideline on Infectious Disease Issues in Xenotransplantation, January 19, 2001, **http://www.fda.gov/cber/xap/docs.htm**

12. Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, February 28, 1997, **http://www.fda.gov/cber/gdlns/ptc_mab.pdf**

13. Manual of Standard Operating Procedures and Policies: Intercenter Consultative/Collaborative Review Process, Version 4, dated June 18, 2004, **http://www.fda.gov/oc/ombudsman/intercentersop.pdf**

14. FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products, dated April 1996, **www.fda.gov/cber/gdlns/comptest.pdf**

15. United States Pharmacopoeia (USP) test method entitled, "<71> Sterility Tests, 27th Edition.

16. ICH Guideline Q5A. Guidance on Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin, (63 FR 51074, September 24, 1998), **www.fda.gov/cber/gdlns/virsafe.pdf**

17. 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 2000, **http://www.fda.gov/cber/gdlns/retrogt1000.htm**

18. ICH Topic Q3. Impurities. (Including guidelines on “Impurities in New Drug Substances”, “Impurities in New Drug Products”, and “Impurities: Residual Solvents”), **http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254**

19. Guideline on Validation of the Limulus Amebocyte Lysate test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices, dated December 1987,
Sections I-IV, **http://www.fda.gov/cber/gdlns/lal.pdf**
Section V, **http://www.fda.gov/cber/gdlns/lalsection5.pdf**
Appendix B, C and D, **http://www.fda.gov/cber/gdlns/lalappendb-d.pdf**
Appendix E, part I, **http://www.fda.gov/cber/gdlns/lalappend_e.pdf**
Appendix E, part 2, **http://www.fda.gov/cber/gdlns/lalappend_e2.pdf**

20. Revisions to the General Safety Requirements for Biological Products, 68 FR 10157, March 4, 2003.

21. ICH Guideline Q5C. Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, November 1995, **http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254**

22. ICH Guideline Q1A(R). Stability Testing of New Drugs and Products (Revised guideline), November 2000, **http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254**

23. Guidance for Industry: Q1E Evaluation of Stability Data, June 2004, **http://www.fda.gov/cber/gdlns/ichstabdta.htm**

24. Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products, dated June 1998, **www.fda.gov/cber/gdlns/stabdft.pdf**

25. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Documentation, dated May 1999, **http://www.fda.gov/cber/gdlns/cntanr.pdf**

26. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications, Revision 1, dated July 1998, **www.fda.gov/cber/gdlns/environ.pdf**

27. Guidance for Industry: Guideline on Sterile Drug Products Produced by Aseptic Processing, dated June 1987, (Reprinted June 1991), **http://www.fda.gov/cder/guidance/old027fn.pdf**

28. Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines), **http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html**

29. Manual of Standard Operating Procedures and Policies Investigational New Drugs; Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications, SOPP8201, Version #3, April 27,1999, **http://www.fda.gov/cber/regsopp/8201.htm**

30. ICH Guideline Q6B. Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, June 1998, **http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254**

31. Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology, dated April 10, 1985, **http://www.fda.gov/cber/gdlns/ptcdna.pdf**

32. Guidance for Industry: IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Information, dated May 2001, **http://www.fda.gov/cber/gdlns/ind052501.htm**