Guidance for Reviewers

Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell 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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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regarding this draft document by the date provided in the *Federal Register* notice announcing the availability of the draft guidance.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, Room 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Additional copies of this draft guidance are available from the Office of Communication, Training, and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling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.

For questions on the content of this draft document contact Darin Weber, Ph.D., at 301-827-5102.

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Contains Nonbinding Recommendations

Draft – Not For Implementation

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GUIDANCE FOR REVIEWERS[1]

Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.

INTRODUCTION

Why Is CBER Issuing This Guidance?

Human somatic cell therapies present a multitude of manufacturing challenges that must be overcome in order to deliver a safe, consistent and potent 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 potential short shelf life of many cellular products, often necessitating the need to release the final product for patient administration before required test results for lot release are available. This guidance provides instructions to you, an FDA reviewer for chemistry, manufacturing, and control (CMC) reviews of human somatic cell therapies, on what information to record and assess as part of your review of an original investigational new drug application (IND), taking into consideration the various manufacturing challenges for these products, such as those mentioned above. FDA reviewers are to use the format of the human somatic cellular 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.

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[1] The CMC review instructions and template described in this guidance reflect minimum current review practice for CMC reviewers in the Division of Cellular and Gene Therapies who are involved in the review of somatic cell therapy INDs. FDA expects to update these CMC review instructions and templates as new information, methods, policies, and technologies become available.

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.

How Will CMC Reviewers of Somatic Cellular Therapy INDs Use This Guidance?

FDA's primary objectives in the review of INDs are to assure the safety and rights of subjects in all phases of investigations and, in Phases 2 and 3, to help ensure 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)). Your review of the IND should assess, given the phase of the investigation, whether sufficient information has been provided to assure the proper identification (identity testing), quality, purity, and strength (potency) of the investigational product (21 CFR 312.23(a)(7)(i)). The human somatic cellular therapy CMC review instructions and template described in this guidance are tools to assist you in your review of human somatic cellular therapy INDs. They are designed to serve as a guide to help ensure that all applicable regulatory requirements are reviewed for 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 as product development proceeds are discussed in *Appendix B.* Relevant regulatory documents are listed in Appendix C. You should also refer to 21 CFR 10.70 for further assistance in understanding documentation expectations.

How Is This CMC Reviewer Guidance Organized?

This 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, instructions are provided to clarify the information you are to document and assess during completion of your CMC review.

I. ADMINISTRATIVE INFORMATION TO BE DOCUMENTED

You should 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
- 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 FDA permission to 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. You should verify that the information being cross-referenced provides the necessary information that otherwise should have been included in the IND. If the letter of cross-reference is not present or the information being cross-referenced does not provide the needed information, the RPM or the CMC reviewer should notify the sponsor to obtain the 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 database search.
- Introduction/rationale: You should summarize relevant information on the development of the product if the sponsor provides this information. In addition, you should document and assess, as appropriate, the sponsor's scientific rationale and justification for using the product for the indication under review.
- Study objectives

II. PRODUCT MANUFACTURING AND CHARACTERIZATION INFORMATION TO BE DOCUMENTED

As described in the following sections, you should document in your review where and how the cell therapy product is manufactured. You also should record all of the components used during the manufacture of the cellular product, such as cells, cell bank systems, and any reagents or excipients. In addition, you should document and assess all procedures used during the manufacturing process.

Examples of these procedures may include procurement and processing of tissue or cells, purification, and other preparation of cells, including final formulation of the product. For further information, refer to the "Guidance for Human Somatic Cell Therapy and Gene Therapy" (Ref. 1) and 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). FDA has also issued a draft guidance for industry on "INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format" (Ref. 3), which you should refer to when it is finalized, along with other final documents listed in Appendix C. You should organize the CMC review using the format and headings described in Appendix A and below, as appropriate.

A. Product Manufacturing – Components

As discussed below, you should describe all components used in manufacturing the cellular product. You also should note the source of each component and summarize the testing performed on each component.

1. Cells

a. Allogeneic and/or Autologous Cell Components

You should document the following in your review:

- Cell source: Tissue and cell type (e.g., colon, hematopoietic, neuronal, T cells)
- Mobilization protocol: Document whether or not donor cells are mobilized or activated *in vivo* in the donor
- Collection method: State the procedure used to obtain cells (e.g., surgery, leukapheresis (indicate device used if possible)) and the name and location of the collection facility
- Donor screening: Evaluate whether screening procedures provide adequate safety and document testing performed. FDA has issued draft guidances for industry on "Class II Special Controls Guidance Document: Human Dura Mater" (Ref. 4), "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 the proposed rule entitled "Suitability Determination for Donors of Human Cellular and Tissue-

Based Products" (Ref. 6). When these are finalized, you should assess whether the donor qualification criteria described in the IND are consistent with those listed in the new guidances or otherwise satisfy the requirements of the new rule.

1) Autologous

If the donor is positive for specific pathogens (e.g., human immunodeficiency virus (HIV), cytomegalovirus (CMV)), or if the donor is not screened, you should document whether the tissue culture methods used during the manufacture of the product could propagate or spread viruses or other adventitious agents to persons other than the autologous recipient.

2) Allogeneic

You should document whether donor screening and testing is being 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, Epstein Barr virus (EBV), and others, as appropriate. In addition, you should document whether FDA-licensed or -approved test kits are used in these detection assays. You should include a description of the type of serological, diagnostic, and clinical history data obtained from the donor. You should 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, you should document testing performed on donor mothers. You should 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

You should document and describe pertinent information relating to the cell bank system used in product manufacture, such as history, source, derivation, characterization, and frequency of testing for each master cell bank (MCB) and working cell bank (WCB), if used. For further information, refer to the document on "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals" (Ref. 7). See also ICH document Q5D, "Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" (Ref. 8). In cases where cell banks have

not been established, such as with some autologous cell products, not all of the testing described below may be possible.

1) Master Cell Bank[2]

You should verify and document that MCB characterization includes testing to adequately establish the safety, identity, purity, and stability of the cells. You also should document and assess whether appropriate testing has been performed to establish the following:

- Product microbiologic characteristics, including sterility, mycoplasma, and *in vivo* and *in vitro* testing for adventitious viral agents, as appropriate (see section III below).

- Freedom from the presence of specific pathogens. Cells of human origin, unless autologous, should be tested for human viruses such as CMV, HIV-1 & 2, HTLV-1 & 2, EBV, HBV, and HCV, as appropriate. You should assess and document testing of cell lines that are exposed to bovine or porcine components (e.g., serum, serum components, trypsin) for bovine and/or porcine adventitious agents.

- Identity of the cells, including tests to distinguish the specified cells through physical or chemical characteristics of the cell line (i.e., phenotype, genotype, or other markers).

- Purity of bank cells: This would include 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).

- You should describe other processes critical to product safety, as applicable. These may include:
    1. Culture conditions used, including documentation of all media, and reagents/components used during production.

[2] 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 a xenotransplantation product. You should refer to the guidances on "Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans" (Ref. 9) and the "PHS Guideline on Infectious Disease Issues in Xenotransplantation" (Ref. 10).

Provide copies of relevant certificates of analysis (COA).

2. Cryopreservation, storage, and recovery of the MCB, including information pertaining to cell density, number of vials frozen, storage temperature, and cell bank location.
3. Genetic and phenotypic stability of the MCB after multiple passages as well as viability of cells after cryopreservation.

2) Working Cell Bank

The working cell bank may have been derived from one or more vials of the MCB. As discussed in the guidance documents referenced above, the amount of information needed to document characterization of the WCB is usually less extensive than MCB. If a two-tiered cell bank system is not established, the sponsor should conduct more extensive testing of the WCB, such as testing for adventitious viral agents. If there is a two-tiered cell bank system in place, you should document the testing of the WCB for:

- Bacterial and fungal sterility
- Mycoplasma
- Limited identity testing

2. Reagents

Under this section, you should list any reagents used in manufacturing the product. For the purpose of this guidance, reagents include 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

You should list in your review all reagents used during product manufacturing including those added to culture media. You should document the following for each reagent:

- Final concentration of the component
- Vendor/supplier

- Source: If a component is human derived, you should document that procedures are in place to assure that no recalled lots were used during manufacture or preparation of the product. For all animal-derived products, you will need to enter in the animal components database the following: source organism, supplier/vendor, country of origin, and stage of manufacture. If porcine products are used, the sponsor should demonstrate that the products are free of porcine parvovirus by including a COA in the submission or other documentation that porcine material has been tested. If a component is derived from a ruminant animal, you should document whether it is from a country where bovine spongiform encephalopathy (BSE) or a substantial risk for BSE exists. If the sponsor uses materials from such a country, discuss obtaining materials from other sources. You also should notify the clinical reviewer of this issue. For more information refer to http://www.fda.gov/cber/BSE/BSE.htm.

- Reagent quality: You should document whether each reagent is an FDA-approved product. If the reagent is regulated as a biologic, drug, or device, you should consider whether a consultative review should be obtained. See section II.3 below for further information about consultative review process. Refer to the guidance on "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" (Ref. 11) for examples of expected information.

- COA or cross-reference letters: If the sponsor is using a research grade (not FDA-approved) reagent as part of the manufacturing process, information verifying the source, safety, and performance of the reagent should be provided in a COA. Alternatively, 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. For COAs, you should assess whether the testing performed is adequate (see "Qualification Program" below) and document in the review any inadequacies in the proposed reagent testing. For letters of cross-reference, you should include the regulatory file number and consider the need for a consultative review to determine if 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. You should document whether a qualification program, which includes safety testing (sterility, endotoxin, mycoplasma, and adventitious agents), functional analysis, purity, and assays to demonstrate absence of potentially harmful substances (e.g., residual solvent testing) is being performed, as appropriate. The appropriate extent of testing will depend on where in the manufacturing scheme the specific reagent is used.

c. Determination of Removal of Reagents From Final Product

The review should contain a description of test procedures performed for detection of residual levels of reagents in the final product. If there are known or potential toxicities associated with these reagents, you should assess whether the sponsor should provide data from a validation study to document their removal prior to initiation of clinical trials.

d. Other Concerns

If beta lactam antibiotics (e.g., penicillins, cephalosporins and related compounds) are used during manufacture, you should consult with the clinical reviewer concerning appropriate exclusion criteria for the study and proper informed consent to address potential patient sensitivity. You also should discuss with the sponsor whether alternative antibiotics should be considered.

3. Combination Products

For purposes of this reviewer guidance, combination products are those human somatic cell therapy biological products that also have a drug or device as part of the final product for which CBER is the lead Center.[3] The drug or device component may have FDA marketing approval (e.g., new drug application (NDA), a premarket approval

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

application (PMA), a 510(k)), it may be investigational (i.e., IND or IDE), or this may be its first use in human clinical trials in this country. You should determine the regulatory status of the drug or device either by contacting the RPM or the sponsor directly, if necessary. If the drug or device has been approved, you should confirm and document this in your review. In most cases, you should request a consultative or collaborative review from the Center for Drug Evaluation and Research (CDER) or the Center for Devices and Radiological Health (CDRH). This is also true for approved drugs or devices, because use in a combination product may result in unapproved uses, such as a new indication, a new dosage, a different route of administration, or, for medical devices, new hardware or software configurations, or unapproved components. You should confer with your supervisor if it is unclear as to 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 MF), the sponsor of the new submission containing the combination product may submit a letter of cross-reference. The letter of cross-reference gives CBER permission to examine the drug or device file for CMC or other information to support the safety of the drug or device and its proposed use as part of the combination product. You should document in your review that a letter of cross-reference from the drug or device file holder is present in the IND and verify that the cross-referenced file contains the needed information. You should inform the consultative or collaborative reviewer that the information referenced in the letter of cross-reference is available to assist with the review.

The request for a consultative or collaborative review should follow the standard operating procedures and policies (SOPP) on the "Intercenter Consultative/Collaborative Review Process" (Ref. 12). The request should specify the questions the reviewer should address and identify the specific sections of the IND that will be needed by the consulting reviewer to address these questions and requested timeline. The requested date for receiving a completed consultative review should be determined in consultation with the consulting review center as it will be based on timeframes mandated by statute, the priority of the consult review request, and workload of the designated consulting 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, it is especially important to work with the RPM to contact the Center/Division to be consulted before sending the consult to identify the appropriate reviewer and ensure that the review can be completed within the time requirements. Also, as described in the SOPP, you should send the Office of Combination Products a copy of the consultative/collaborative request for monitoring/tracking purposes. You or the RPM should follow up with the consulting reviewer to confirm that essential documents are received along with the consultative

review request. If problems that impact the timeliness of the consultative review occur during the consult review period, you should 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.

a. Review of Device

In the device consultative/collaborative review request, you should describe the device component in the combination product and where to find information in the submission. You should ask the CDRH reviewer to identify concerns with how the device component will be used in the combination product, to determine whether appropriate types of biocompatibility and other normally required device testing were adequately performed, and to assess testing of any hardware and software controlling the hardware. In addition, if the sponsor asserts barrier or performance claims, you should determine what information the CDRH reviewer should assess related to these claims. You should attach the CDRH review of the device component(s) to your review and communicate any outstanding issues to the sponsor. You also should document basic information concerning the device components of the combination product, such as the device name, vendor or source, purpose, regulatory status, and a brief description of the device.

b. Review of Drug Components

In the drug consultative/collaborative review request, you should describe the drug component in the combination product and state where to find information on the component in the submission. The drug component of a combination product, whether approved or investigational, is likely to have a novel route of administration, a different dosage, or a new clinical indication. You should ask the CDER consult reviewer to identify concerns with how the drug will be used in the combination product and also to evaluate the methods of manufacturing and the adequacy of results from testing of the drug substance and/or drug product. You should 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 for the particular submission. You should attach the review obtained from the CDER reviewer to your review and communicate any outstanding issues to the sponsor, as appropriate.

4. Summarize Any Areas of Concern That Need to Be Addressed

You should summarize any areas of concern identified during the review of the product components. You should discuss these concerns with the sponsor and/or communicate in a letter to the sponsor, as described in section X below.

B. Product Manufacturing – Procedures

In this section of your review, you should include a detailed description of all procedures used during the production and purification of the cellular therapy product. A schematic of the production and purification process and in-process and final product testing is often helpful; if provided by the sponsor, you should append it to the IND review.

1. Preparation of Autologous or Allogeneic Cells

You should include the following documentation in your review:

a. Method of Cell Collection/Processing/Culture Conditions

The review should document the volume and number of cells collected. You should include any mechanical or enzymatic digestion steps used or use of any cell selection device or separation device, including density gradients, magnetic beads, or fluorescence activated cell sorting (FACS). You also should include a description of culture systems (flasks, bags, etc.) and state whether the system is closed or open. You should describe any in-process testing.

b. Irradiation

If the autologous or allogeneic cell product is irradiated before injection, you should document the data provided in the submission to demonstrate that the cells are rendered replication-incompetent. You should review evidence and document that the cells still maintain their desired characteristics after irradiation. You should document information regarding the calibration of the cell irradiator source.

c. Process Timing & Intermediate Storage

You should include in the review an estimate of the 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, you should include this