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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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regarding this draft document by the date provided in the *Federal Register* notice announcing the availability of the draft guidance.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Additional copies of this draft guidance are available from the Office of Communication, Training, and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling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

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
August 2003

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Draft – Not For Implementation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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.

[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

information along with any stability studies initiated (see section V.A.1 below). You should document the time and conditions of storage between cell collection and final harvest. You should record whether there are adequate procedures in place to ensure the stability of the bulk harvest while in storage.

2. Final Harvest

You should document whether the final cell harvest is centrifuged prior to final formulation, and if so, you should describe the wash conditions and media used. You should document whether the cells are cryopreserved after formulation or formulated immediately and given to the patient. If the final harvest is stored, you should describe the storage conditions and the length of storage.

3. Final Formulation

You should document the formulation of the final product in the review. You should record 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.2 above). You should document the vendor and final concentration of these proteins. You also should record the cell density or concentration used in the final product. If the final product is delivered to the clinical site frozen, you should include in the review a description of how the product will be shipped and data to show that the product can be thawed with consistent results.

4. Product Manufacturing Concerns That Need to Be Addressed

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

III. PRODUCT TESTING

Product testing for cellular therapies includes, but is not limited to, microbiological testing (including sterility, mycoplasma, and adventitious viral agent testing) to assure safety and assessments of other product characteristics such as identity, purity (including endotoxin), viability, and potency. You should verify that the sponsor will or has performed appropriate testing throughout manufacturing, including manufacture of cell banks, to evaluate the manufacturing process itself and to insure the quality and consistency of the product lots. 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. You should refer to "FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-

Derived Products" (Ref. 13) for additional information. For this section of the IND review, you should describe the specifications used for intermediate 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. You should assess the appropriateness of acceptance criteria based on any results previously obtained by the sponsor. You also should ensure that the proposed specifications are appropriate to the stage of product development, because release criteria should be refined and tightened as product development progresses toward licensure (see Appendix B). Release tests and specifications should include, but are not limited to, the following:

A. Microbiological Testing

You should verify that the sponsor will perform microbiological testing on cell banks, in-process intermediates, and the final product, as appropriate.

1. Sterility Testing (Bacterial and Fungal Testing)

The following information is provided to instruct you on current practices for sterility testing.

a. Test Method

You should verify that the sponsor will perform sterility testing on the final product. Suitable tests include the test described in 21 CFR 610.12 and the test described in United States Pharmacopoeia (USP) <71> Sterility Testing (Ref. 14). If the sponsor is using another test method, you should assess the adequacy of this alternative test method and 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 prior to product licensing pursuant to 21 CFR 610.9. If antibiotics are used in product manufacturing, you should verify that the antibiotics were removed prior to sterility testing. If the antibiotics cannot be removed, you should assess the validity of the sterility assay using the bacteriostasis and fungistasis testing as described in USP <71> Sterility Tests. This assay should be performed to ensure that any residual antibiotic present in the product does not interfere with the results of sterility testing.

b. Test Timing

Sponsors frequently perform in-process sterility testing at critical points during manufacturing. For example, this might be done routinely during extended culture periods and after critical points in manufacturing, such as when cells have

undergone activation or other modification. You should document in the review whether in-process testing is done. You also should assess whether proposed in-process testing is appropriate based on the manufacturing scheme and discuss this with the sponsor as needed. The test method used for in-process sterility testing is at the discretion of the sponsor.

The results of this test should meet acceptance criteria as part of required final product specifications. If the final product is frozen prior to use, the sponsor should perform testing on the product prior to cryopreservation with results available prior to patient administration. However, if the product undergoes manipulation (e.g., washing, culturing) after thawing, particularly if procedures are performed in an open system, the sponsor might need to repeat sterility testing. If cells must be administered prior to obtaining the results from 14-day sterility testing, you should ensure that the sponsor performs sterility testing on a sample taken 48-72 hours prior to final harvest or after the last re-feeding of the cultures and that the sponsor checks the cultures prior to release of the product. This test should be continued for the full 14 days even after the product has been given to the patients. If the results from a 14-day sterility test are not available prior to patient administration, you should ensure that the sponsor performs a gram stain and a final sterility test on the final formulated product. To assure safety, the sponsor should use the no-growth result from the 48-72 hour sterility test and the negative gram stain for release criteria. You also should document and assess the procedures that the sponsor will use if ongoing sterility results show that the product the patient received was contaminated. Since such contamination would suggest a significant risk for human subjects, such procedures must include notification to FDA and all participating investigators in accordance with 21 CFR 312.32(c).

2. Mycoplasma

You should confirm that mycoplasma testing is being performed on the product when there is the best chance of detecting contamination, such as after pooling of cultures but prior to cell washing. You should document that testing is being conducted on both cells and supernatant. 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. You should document whether there is in-process testing for mycoplasma during extended culture procedures. Due to the limited shelf life of many cellular therapy products, it is frequently not feasible for a sponsor to perform the recommended culture-based assay (Ref. 7) for release testing. In these cases, the use of polymerase chain reaction (PCR)-based mycoplasma assays is acceptable during product development. However, you

should discuss with the sponsor that prior to product licensing, data should be provided to demonstrate that the PCR test has adequate sensitivity and specificity.

3. Adventitious Agent Testing

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. 15) and Ref. 7.

a. *In Vitro* Viral Testing

When cell lines are used, you should document that *in vitro* viral testing is conducted on the MCB and end of production cells (one-time test). This assay is carried out by inoculation of the test article into various susceptible indicator cell lines. The choice of cells used depends on the species of origin of the product to be tested. The test should include monolayer cultures of the same species and tissue as that used for production of the product, as well as a human and/or a non-human primate cell line susceptible to human viruses. In addition, the test should include a measure of both cytopathic and hemadsorbing viruses. You should document the cell lines used in the review.

b. *In Vivo* Viral Testing

When cell lines are used, you should document that *in vivo* viral assays were conducted on the MCB. These tests are carried out by inoculation of the test sample into animals such as adult and suckling mice and embryonated hen eggs. In some cases, additional testing of guinea pigs, rabbits, or monkeys may need to be included. These assays measure the test animals for any indication of illness. You should document in the review the animals used by the sponsor. The sponsor should provide an assessment of the results of such testing, which you should summarize in your review.

c. Selected Species-Specific Testing for Adventitious Viruses

You should document what specific adventitious agent testing is done at the different stages of manufacturing (e.g., cell banks, final product) and the test methods used. In addition, you should document whether FDA licensed/approved/cleared test kits were used. Since human cell lines are used as the therapeutic product, there should be documentation of testing for human pathogens. Human viral agents can be tested using a PCR-based test system. Tests for CMV, HIV-1 & 2, HTLV-1 & 2, EBV, HBV, HCV, and other human viral agents should be included, as appropriate.

B. Identity

You should ensure that the sponsor verifies 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. If the final product consists of one or more cell lines, you should ensure that the sponsor documents whether there are tests in place to distinguish between the multiple cell lines used. Identity testing for the MCB should include testing to distinguish between multiple cell lines used to produce a single final product. These tests might include assays for cell surface markers or genetic polymorphisms (see Ref. 1 for additional information). 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.

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). Testing for purity 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

You should document testing for purity of a cell therapy product including assays for residual peptides, proteins, and reagents used during manufacture, such as cytokines, growth factors, antibodies, and serum. This should also include a measurement of contaminating cell phenotypes or cell debris. For further information, you should refer to ICH Q3 on "Impurities" (Ref. 16).

2. Pyrogenicity/Endotoxin

Endotoxin testing using the Limulus Amebocyte Lysate (LAL) assay method is typically done as an alternative to pyrogenicity testing (see 21 CFR 610.13(b)) for early-phase trials. If the sponsor is using the LAL endotoxin method, you should inform the sponsor that, for licensure, the LAL endotoxin test must be shown, as explained in 21 CFR 610.9, to be equivalent to that of the pyrogenicity test described in 21 CFR 610.13(b). For any parenteral drug, except those administered intrathecally, FDA guidance recommends that the upper limit for endotoxin be 5 EU/kg body weight/dose. Intrathecally administered drugs have a lower limit of 0.2 EU/kg body weight/dose. However, specifications should be based on the sponsor's 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. 17). You should 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 release.

D. Potency

A suitable potency assay should be a measure of the relative biological function of the product. You should document and assess all assays used to measure potency. These assays should be quantitative, but in addition, they may include a qualitative biological assay. By the end of Phase 2, the sponsor should have in place a potency assay, consisting of *in vivo* or *in vitro* tests, that measure an appropriate biological activity. This assay should be validated by licensure.

E. Other

1. General Safety

Cellular therapy products are exempt from general safety testing under 21 CFR 610.11(g)(1).

2. Viability

You should ensure that minimum release criteria for viability has been established. For somatic cellular therapies, the minimum acceptable viability specification is generally set at 70 percent. If this level cannot be achieved, you should inform the sponsor that data should be submitted demonstrating that dead cells and cell debris do not affect the safe administration of the drug and/or the therapeutic effect, to support the lower viability specification. For further information, see Ref. 1.

3. Cell Number/Dose

As part of the product testing and release, you should ensure that there are specifications for the minimum number of viable and functional cells. You also should document whether a maximum number/dose of cells to be administered has been established and on what basis.

IV. FINAL PRODUCT RELEASE CRITERIA TESTING

The final product is defined as the final formulated product used for patient administration. The IND review should include a tabulation of the sponsor's proposed specifications (tests, test methods, and acceptance criteria), including test sensitivity and specificity, where appropriate, for the final product. Tests should include assays to ensure the safety, purity, potency, and identity of the product (see section III above). You should confirm that final product release criteria testing is 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. You should clearly indicate in the review additional final product tests whose results will not be available prior to release, together with their specifications, and include a description of the reporting notification process if the acceptance criteria are not met.

V. PRODUCT STABILITY

The objective of stability testing during early phases of the clinical trial is to establish that the product is sufficiently stable for the time period required by the study (21 CFR 312.23(a)(7)(ii)). For later phases of clinical investigation, you should inform the sponsor of the need to expand upon this initial stability information and to begin collecting information needed to develop a final formulation and dating period. You should document and assess the product development plan in the IND review to determine how much stability data is needed for the current phase of investigation. You should assess the stability indicating assays, which may be different from final product release criteria test methods, for adequacy as indicators of product stability. You should document what stability measures were used to support the Phase 1 study. For further information, refer to ICH Q5C: "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products," (Ref. 18), ICH Guideline Q1A(R): "Stability Testing of New Drugs and Products" (revised guideline) (Ref. 19), ICH Guideline Q1E: "Evaluation of Stability Data" (Ref. 20), and when finalized, the draft guidance on "Stability Testing of Drug Substances and Drug Products" (Ref. 21).

Stability Protocol Tests

Stability testing protocols may be appropriate for both in-process material and the final cellular product. If submitted, a sponsor's proposed stability protocol should include a measure of product sterility, identity, purity, quality, and potency. For each test proposed by the sponsor, you should document in the review the test method, sampling time points (there should be a

zero-time point), testing temperature, and other appropriate information, including the adequacy of the assays used to indicate product stability. The stability program should measure the above parameters for the duration of storage required by the clinical protocol or planned further development. You should include preliminary data in the review if submitted.

1. In-Process Stability Testing

If the cells are cryopreserved, you should document the existence of a stability protocol 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. You also should document any stability testing performed on the product during the holding steps, such as cryopreservation of cells. You should assess whether the time period that the sponsor has established is appropriate.

2. Final Product Stability Testing

You should document and assess any data provided which demonstrate that the product is stable between the time of product formulation and patient infusion, to establish an expiration dating period. You should verify that the sponsor is conducting the testing at the appropriate temperatures and at time points consistent with predicted storage times. You should inform the sponsor of the need to develop validation studies during Phase 3, using conditions that stress the system. If the product is shipped from the manufacturing site to the clinical site, you should ensure that the sponsor documents the time and shipping conditions (i.e., packaging, temperature). You should also assess whether the stability protocol is adequate to demonstrate that product integrity, sterility, and potency are maintained under the proposed shipping conditions. If necessary, you should notify the sponsor that validation studies should be initiated by Phase 3 and completed prior to submission of a biologics license application (BLA).

VI. OTHER ISSUES

A. Product Tracking

For autologous or patient-specific products, the sponsor should have in place a plan to track the therapeutic product from collection to administration of the product and procedures to ensure that the product is segregated from other products in incubators, hoods, and cryopreservation units. You should describe and assess the adequacy of the sponsor's product tracking and segregation system in your review.

B. Labeling

You should document whether there is precise labeling that ensures that the product reaches the proper clinical site if more than one site is involved in the study. In addition, there should be documentation included in the review that describes product labeling throughout the manufacturing process. You should verify that any proposed labeling contains the date of product manufacture, storage conditions, expiration date and possibly time, product name, and patient identifiers. For autologous cell therapies, two unique patient identifiers should be used to minimize the potential for any mix-ups. In addition, as described in 21 CFR 312.6, the label for an investigational product must contain the following statement: "Caution: New Drug – Limited by Federal law to investigational use." For autologous cell therapies, if the donor was not screened or tested for adventitious agents, or if no testing was performed on the cellular product, it is recommend that labeling should carry the warning "Not Tested for Biohazards." For more information refer to Ref. 6, when finalized. To be licensed, the labeling of the final product container and package must conform to the requirements in 21 CFR 610.60-65.

C. Container/Closure

You should include in the IND review a description of the types of container and closure being used. You also should record whether the container used is compatible with the product. For more information, see Ref. 2 and, when finalized, Ref. 3.

D. Environmental Impact

Under 21 CFR 312.23(a)(7)(iv)(*e*), the sponsor 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). You should document in your review your assessment of any extraordinary circumstances. See the guidance on "Environmental Assessment of Human Drug and Biologics Applications" (Ref. 22) for additional information.

E. Validation and Qualification of the Manufacturing Process and Facility

The manufacturing process for somatic cell 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 appropriate controls are in place for monitoring manufacturing consistency and product quality are key elements in ensuring patients receive a safe, consistent, and potent product. Consequently, prior to production of clinical lots and initiation of clinical studies, procedures must be in place to ensure proper manufacturing oversight as outlined in 21 CFR 211.22 in the current good manufacturing practice (cGMP) regulations. This includes programs for product manufacturing quality assurance (QA) and quality control (QC), and the identity of responsible individuals and their duties. In your review, you should describe and assess the adequacy of the sponsor's quality program, including procedures for preventing, detecting, and correcting deficiencies that may compromise product integrity or function or may lead to the possible transmission of adventitious infectious agents.

You should document the changeover procedures described in the IND and ensure that no cross-contamination occurs among an individual patient's cells and other products produced in the same facility. These procedures should be in place by Phase 1 and should include, but are not limited to: area clearance, cleaning and decontamination reagents and rationale for their selection, and segregation of activities. In addition, you should document that aseptic processing steps have been adequately validated. With most cellular therapies, the manufacturing process should be conducted under aseptic conditions due to the lack of final sterile filtration of the product prior to patient infusion. To validate that the process consistently produces a sterile product, media should be substituted for the product and then taken through all steps in the process. You should obtain consultative reviews from the Division of Manufacturing and Product Quality to assess any data submitted by the sponsor. In addition, you should refer to the "Guideline on Sterile Drug Products Produced by Aseptic Processing" (Ref. 23) for further information. You should inform the sponsor that prior to licensure, the facility and all processes used to manufacture the product must be validated.

F. Biostatistics

In CMC IND reviews, 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. You should 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. If applicable, you should

document in your review recommendations from the Biostatistics consult.

VII. PRECLINICAL STUDIES

You should document information provided by the sponsor to support the scientific rationale underlying the proposal. This section should contain 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.

VIII. CLINICAL STUDIES

You should provide a brief description of the following in the CMC review:

A. Protocol Title

B. Patient Population

C. Route of Administration

D. Dose

This should include the dosing regimen and whether there is a dose escalation. You also should document the dosing range and the number of patients enrolled in each dose. You should note whether the dose escalation is intra-patient or inter-patient and what time interval/data evaluations occur between dose increases.

E. Frequency

This should include the frequency of dose injections per treatment cycle and the number of proposed cycles.

F. Genetic and Biochemical Testing

You should assess, in conjunction with the clinical reviewer, whether all genetic and/or product-specific biochemical testing being done on the patient is appropriate and whether the test has been appropriately developed and validated for the stage of clinical investigation. You also should 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.

IX. RECOMMENDATION

Based on your review of the IND submission, you should describe any information that is missing or incomplete and any issues that require additional clarification. You also should provide an overall assessment, from the CMC perspective, of whether the trial may proceed. You should document all additional information obtained from the sponsor through telephone conversations or faxes. You should note this documentation in the Recommendation Section of the Product Review Template, throughout the review document, or as an attachment to the review. Upon completion, you should sign and date the review and then obtain concurrence from your supervisor.

X. COMMENTS TO SPONSOR

You should draft comments on unresolved issues that should 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. 24), for additional information. You should 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 fit the criteria listed in § 312.42(b).

B. Non-Clinical Hold

These are comments that the sponsor should 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.

Effective Date

Insert signature date

Appendices

Appendix A – Product Review Template (Somatic Cell Therapy)
Appendix B – Review Considerations for Development of Final Product Release Criteria Specifications and Stability Protocols
Appendix C – Relevant Regulatory Documents

Appendix A - Product Review Template

Product Review Template (Somatic Cell Therapy)

PRODUCT REVIEW (Somatic Cell)

Supervisor Concurrence/Date

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

KEY WORDS:

INTRODUCTION / RATIONALE:

STUDY OBJECTIVES:

PRODUCT MANUFACTURING AND CHARACTERIZATION:

Product Manufacturing - Components

Cells

Allogeneic or Autologous Cell Components

Cell Source:

Method of Collection:

Donor Screening:
Description

Tabulation of Testing

Cell Bank System - If Applicable

Master Cell Bank (MCB)
Description

Tabulation of Testing

Working Cell Bank (WCB)
Description

Tabulation of Testing

Reagents

Tabulation of Reagents Used in Manufacture

Reagent/Excipient	Final Concentration	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

Preparation of Autologous or Allogeneic Cells

Method of Cell Collection/Processing/Culture Conditions

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

PRODUCT TESTING

In-Process Testing And Criteria

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

Test	Method	Specification	Sensitivity	Specificity
Sterility				
Mycoplasma				
Purity (endotoxin)				
Purity (other contaminants)				
Identity				
Potency				
Others (cell dose,)				
Others (cell viability)				

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

Description of Test Methods

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 of the Manufacturing Process

Biostatistics

PRECLINICAL STUDIES

CLINICAL STUDIES

Protocol Title

Patient Population

Route of Administration

Dose

Frequency

Genetic and Biochemical Testing

RECOMMENDATION

COMMENTS TO SPONSOR

Clinical Hold

Non-Clinical Hold

Signature

Reviewer Name

Date:_____

Appendix B - Review Considerations for Development of Final Product Release Criteria Specifications and Stability Protocols

The following are some general considerations to take into account during your review of the submission. 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. 25). It is expected that certain release specifications, such as those related to product safety, be in place prior to initiating Phase I clinical studies. As product development proceeds, additional specifications for product quality and manufacturing consistency should be implemented. For additional discussion of manufacturing quality control, see Guidance for Industry: Guideline on the Preparation of Investigational New Drug Products (Ref. 26) and Guidance for Industry: IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information (Ref. 27).
The following considerations, in addition to those outlined in 21 CFR 312.23(a)(7), should be helpful in assessing the sponsor's proposed final product release criteria program:

- Have specifications been developed that are appropriate for the stage of product development?
- Are the product characterization assays appropriate for the particular stage of product development?

A. Development of Release Acceptance Criteria

You should assess the sponsor's proposed release acceptance criteria for the final product 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 – Refined 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

You should assess the sponsor's proposed analytical procedures keeping the following considerations in mind:

- Phase 1 – 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, you should verify that the sponsor intends to

initiate validation of alternative method to be of equal sensitivity and specificity or advise the sponsor of the need to do so.
- Phase 3 – Validation of analytical procedures should be ongoing or complete and dependent on data generated during clinical studies.
- Licensure – The product specification should be in place and established under a validated assay.

For further information on specific analytical procedures, refer to section III of this guidance ("Product Testing").

C. Development of Stability Protocols

You should assess the sponsor's plans for determining the stability of the final product as described below:

- Phase 1 – You should determine whether preliminary data on product stability is available to indicate whether the product or components are likely to remain stable for the duration of the clinical trial.
- Phase 2 – You should determine whether the sponsor has initiated a stability protocol or been advised to do so to accumulate additional data to demonstrate stability for the duration of the clinical trial.
- Phase 3 – Data from stability protocols should be used to establish the dating period, storage conditions, and shipping conditions.

For further information on stability protocols and testing, refer to section V of this guidance ("Product Stability").

Appendix C - Relevant Regulatory Documents

Most documents are available for downloading from www.fda.gov/cber/guidelines.htm.

1. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy. March 1998. http://www.fda.gov/cber/gdlns/somgene.pdf
2. Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products. November 1995. http://www.fda.gov/cder/guidance/phase1.pdf
3. Draft Guidance for Industry: INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry Manufacturing and Controls Content and Format. February 1999. http://www.fda.gov/cber/gdlns/indbiodft.htm
4. Class II Special Controls Guidance Document: Human Dura Mater; Draft Guidance for Industry and FDA. October 22, 2002. 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). June 2002. http://www.fda.gov/cber/gdlns/cjdvcjd0602.htm
6. Proposed Rule: Suitability Determination for Donors of Human Cellular and Tissue-Based Products. September 30, 1999. 64 (FR 52696). http://www.fda.gov/cber/rules/suitdonor.pdf
7. Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals. July 12, 1993. http://www.fda.gov/cber/gdlns/ptccelllines.pdf
8. ICH Guideline Q5D: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products. July 1997. http://www.ich.org/pdfICH/q5d.pdf
9. Guidance for Industry: Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans. April 2003. http://www.fda.gov/cber/gdlns/clinxeno.htm
10. PHS Guideline on Infectious Disease Issues in Xenotransplantation. January 19, 2001 http://www.fda.gov/cber/gdlns/xenophs0101.htm
11. 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
12. Manual of Standard Operating Procedures and Policies: Intercenter Consultative/Collaborative Review Process. February 2003. http://www.fda.gov/oc/ombudsman/intercentersop.pdf
13. FDA Guidance Concerning Demonstration of Comparability of Human Biological Product, Including Therapeutic Biotechnology-derived Products. April 1996. www.fda.gov/cber/gdlns/comptest.pdf
14. United States Pharmacopoeia (USP), Chapter <71> Sterility Tests, 26th Revision, 2003. www.usp.org
15. ICH Guideline Q5A: Guidance on Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin. March 1997. http://www.ich.org/pdfICH/q5a.pdf
16. 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/ich5q.html#Impurity

17. 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. 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
18. ICH Guideline Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. November 1995. http://www.ich.org/pdfICH/q5c.pdf
19. ICH Guideline Q1A(R): Stability Testing of New Drugs and Products (Revised guideline). November 2000. http://www.ich.org/pdfICH/q1arstep4.pdf
20. ICH Guideline Q1E: Evaluation of Stability Data. February 2002. http://www.ich.org/pdfICH/Q1Estep2.pdf
21. Draft Guidance for Industry, Stability Testing of Drug Substances and Drug Products. June 1998. www.fda.gov/cber/gdlns/stabdft.pdf
22. Guidance for Industry: Environmental assessment of Human Drug and Biologics Applications. July 1998. www.fda.gov/cber/gdlns/environ.pdf
23. Guideline on Sterile Drug Products Produced by Aseptic Processing. June 1987. http://www.fda.gov/cder/guidance/old027fn.pdf
24. Manual of Standard Operating Procedures and Policies (SOPP 8201); "Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications. April 27, 1999. http://www.fda.gov/cber/regsopp/8201.htm
25. ICH Guideline Q6B: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. March 1999. http://www.ich.org/pdfICH/Q6bstep4.pdf
26. Guidance for Industry: Guideline on the Preparation of Investigational New Drug Products (Human and Animal). November 1992. http://www.fda.gov/cder/guidance/old042fn.pdf
27. Guidance for Industry: IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information. May 2001. http://www.fda.gov/cber/gdlns/ind052501.htm