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