

BRIEFING DOCUMENT

UPDATE ON SOMATIC CELL THERAPY LETTER

Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

**Center for Biologics Evaluation and Research
Food and Drug Administration**

**April 11, 2008
Hilton Hotel, Gaithersburg Maryland**

INTRODUCTION

Since 2002, the Office of Cellular, Tissue, and Gene Therapies (OCTGT) has issued a letter to the sponsor of each somatic cell therapy (SCT) investigational new drug application (IND) to request submission of information on product manufacturing quality control procedures, product testing, and clinical trial oversight and monitoring practices. Through the review of IND and Master File submissions and inspections of both manufacturing facilities and clinical sites, we had noted a number of recurring deficiencies concerning product manufacturing quality control systems and clinical trials oversight and monitoring. Thus we issued the somatic cell therapy letter (SCTL) to request information so that we could assist sponsors in identifying and correcting deficiencies to enhance the safety of SCT products and facilitate product development plans. The goals of review of the submitted information were the following:

- To ensure that all SCT products in ongoing clinical trials meet our current expectations for release testing, product characterization, clinical trial oversight and monitoring,
- To identify lapses in product testing with potential safety implications
- To obtain information concerning product characterization and manufacturing processes to assist sponsors in moving these products toward licensure,
- To encourage the development of clinical trial monitoring programs that would adhere to Good Clinical Practice,
- To encourage the submission of final study reports,
- To gather information concerning the need for development of additional guidance and/or other regulatory documents, and
- To determine the need for other forms of outreach to SCT sponsors.

This briefing document summarizes our review experience and factors supporting our conclusion that requesting responses to the SCTL is no longer necessary.

THE SOMATIC CELL THERAPY LETTER (SCTL):

The SCTL was based on the experience of a similar letter for gene therapy INDs. OCTGT issued a “Dear Gene Therapy Sponsor” (referred to as the Gene Therapy Letter) letter on March 6, 2000 following the death of a subject in an adenoviral vector clinical trial. The purpose of the Gene Therapy Letter was to request submission of information to allow CBER to review status of all gene therapy trials and address any safety concerns.

OCTGT determined that a similar exercise would be beneficial for SCT INDs since the field was more diverse, older, and had less public scrutiny, as there is no equivalent of the NIH OBA/RAC. Review experience had indicated that many SCT IND sponsors were not fully aware of the current regulatory requirements for manufacturing a product and conducting a clinical trial. Thus a SCTL was felt to be a useful tool to allow review and address any safety concerns.

The SCTL was issued beginning in June 2002 and was addressed individually to each IND sponsor. The requested date for response was 60 days from anniversary date of the file. Lack of response was not considered cause for placing the file on clinical hold. The letter consisted of 8 multi-part Chemistry, Manufacturing and Controls (CMC) questions and 3 multi-part Clinical questions.

CMC questions

The 8 CMC questions in the SCTL addressed the following topics:

- QC/QA program –description, procedures, personnel, audits
- Qualification of starting cells, reagents, equipment- safety and quality
- Tracking, segregation, labeling
- Cleaning and sanitization
- Procedures to control contamination and cross contamination
- Processing and testing timeline
- In-process testing methods
- Lot release testing methods
- Sterility validation, aseptic processing- action plan, investigations
- Product characterization
- Stability program
- Cross referenced files
 - files crossed referenced to this file
 - files crossed referenced by this file

Clinical Questions

The 3 Clinical questions in the SCTL addressed the following topics:

- A complete description of the clinical monitoring program including:
 - A description of the personnel responsible for monitoring
 - A summary of the procedures for clinical study conduct monitoring and auditing
- A recommendation that final study reports be submitted for all studies

REVIEW SUMMARY

Responses to the SCTL were reviewed by the assigned IND review team, to assess whether ongoing clinical trials met our current expectations and to identify lapses in product safety testing. The responses did not identify a large number of safety issues; safety issues that were identified for a specific IND were addressed between the review team and the IND sponsor. Through the review of SCTL responses we obtained current information on the status of product characterization and manufacturing processes, and identified a strong need for additional guidance documents and other forms of outreach to SCT sponsors.

The experience of SCTL response review directly contributed to the development of multiple guidance documents. Several of these have been published and others are in progress. Relevant to CMC, guidance documents on IND submission and review and rapid microbiology test methods have been published. “Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs)” was published in August 2003. This guidance is in the process of finalization as a Guidance for Industry and Reviewers, and will address the data and information that sponsors should provide in an IND submission and a template that can be followed by both sponsors and OCTGT CMC reviewers. OCTGT was the lead in developing “Draft Guidance for Industry: Validation of Growth-Based Methods for Sterility Testing of Cellular and Gene Therapy Products” in response to the broad interest in alternative

methodologies to traditional sterility test methods. OCTGT also contributed to FDA Guidances that have sections on special considerations for SCT products, most notably, “Draft Guidance for Industry: INDs- Approaches to Complying with CGMP During Phase 1” and “Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing- Current Good Manufacturing Practice.”

OCTGT has a number of guidance documents in preparation. In the CMC area, a guidance document on potency, which was the topic of the CTGTAC meeting in February 2006, is currently under development. In the clinical area, one example is a guidance document tentatively titled “Clinical Study Design for Early Phase Studies of Cellular and Gene Therapies”, which will provide recommendations concerning trial design, safety monitoring and the use of clinically relevant and reproducible endpoints. Guidance in the area of good clinical practice is provided to sponsors by “ICH E6: Good Clinical Practice: Consolidated Document.

In addition to guidance documents, strong efforts have been made to increase and improve outreach through presentations at conferences and holding liaison meetings. As part of our outreach program, we have made sponsors aware of existing guidances concerning Good Clinical Practice (see Appendix). CMC talks commonly focus on product characterization and potency. OCTGT gives regulatory presentations at numerous conferences each year, which reach broad and differing audiences. OCTGT has served on the organizing committee and given numerous regulatory talks each year at the ISCT Somatic Cell Therapy Symposium. This meeting has a regulatory and training focus for an audience directly involved in product manufacture for IND submission.

Another topic of outreach has been the regulations in 21 CFR 1271, commonly referred to as the “Tissue Rules,” that were finalized and went into effect in May 2005. The Tissue Rules focus on the prevention of transmission of infectious disease , and 21 CFR 1271 Parts A-D apply to SCT products. Further information on donor testing and screening can be found in Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), published in August 2007.

OVERALL CONCLUSIONS

Our experience in reviewing the data from SCTL responses has resulted in multiple guidance documents, issued and in preparation, and in numerous outreach activities broadly applicable to the field of cell therapies. With the availability of guidance documents to address our expectations for IND submissions and clinical trial conduct, it is not necessary to convey these expectations and request responses in a separate format. Therefore, we will discontinue issuing the SCTL and no longer request that sponsors provide updates in the format of the SCTL questions. Updates can be provided in information amendments or annual reports, as appropriate.

APPENDIX

REFERENCES FOR THE REGULATORY PROCESS FOR THE OFFICE OF CELLULAR, TISSUE AND GENE THERAPIES (OCTGT)

<http://www.fda.gov/cber/genadmin/octgtprocess.htm>

GUIDANCE DOCUMENTS

Guidances directly relevant to SCT CMC issues:

- Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs) (8/15/03)
<http://www.fda.gov/cber/gdlns/cmcsomcell.htm>.
- Draft Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (11/8/04)
<http://www.fda.gov/cber/gdlns/gtindcmc.htm>.
- Draft Guidance for Industry: Validation of Growth-Based Methods for Sterility Testing of Cellular and Gene Therapy Products (2/11/08)
<http://www.fda.gov/cber/gdlns/stercgtp.htm>.
- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), (8/24/07)
<http://www.fda.gov/cber/gdlns/tissdonor.htm>.

Guidances concerning Good Clinical Practice in FDA Regulated Clinical Trials:

Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance
Links to FDA regulations, all final and draft guidances, and conferences/workshops on Good Clinical Practice are available at www.fda.gov/oc/gcp/default.htm

Guidances with sections on considerations for cell and gene therapy products:

- Draft Guidance for Industry: INDs- Approaches to Complying with CGMP During Phase 1. (1/12/06) <http://www.fda.gov/cber/gdlns/indcgmp.pdf>
- Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing- Current Good Manufacturing Practice (9/24/04)
<http://www.fda.gov/cber/gdlns/steraseptic.pdf>.

Guidances in development:

- Potency Assays for Cell and Gene Therapy Products.
- Clinical Study Design for Early Phase Studies of Cellular and Gene Therapies