

**Food and Drug Administration
Center for Biologics Evaluation and Research
Cellular, Tissue and Gene Therapies Advisory Committee**

**SUMMARY MINUTES
Meeting #41, February 9-10, 2006
Hilton Hotel, Gaithersburg, MD**

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The summary minutes for the February 9-10, 2006 meeting of the Cellular, Tissue and Gene Therapies Advisory Committee were approved on September 28, 2006.

I certify that I attended the meeting of the Cellular, Tissue and Gene Therapies Advisory Committee on February 9-10, 2006 and that this report accurately reflects what transpired.

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Gail Dapolito, Executive Secretary

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James Mulé, Ph.D., Chair

SUMMARY MINUTES

The Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) met on February 9, 2006 at the Hilton Hotel, Gaithersburg, MD. In open session, the committee discussed issues related to potency measurements for cell and gene therapy products.

On February 9, James Mulé, Ph.D., Chair, called the meeting to order and introduced the members, consultants and guests. The Executive Secretary read the conflict of interest statement into the public record. This statement identified members and consultants of the committee with an appearance of a financial conflict of interest, for whom FDA issued waivers to participate. Copies of the waivers are available from the FDA Freedom of Information Office.

The FDA provided an introduction to the challenges and regulatory considerations related to the development of meaningful and relevant potency assay measurements for cell and gene therapy products. Guest speakers provided presentations related to practical aspects of bioassay development, analysis and validation in the context of an automated quantitative microscopy method and potency assays for plasmid-based therapeutics, adenovector-based therapies, mesenchymal stem cell therapies, viral vaccines and autologous immunotherapy.

During the Open Public Hearing the Committee received comments from firms involved in the development of potency assays for cell and gene therapy products and from an individual speaking about cancer.

Following the Open Public Hearing the Committee discussed questions from the FDA related to the following issues:

- Assay Design and Validation
- Correlation Studies
- Incorporating State-of-the-Art Technologies
- Cutting Edge Technologies and Future Research Needs

Assay Design and Validation

The Committee was asked to discuss design schemes for cellular and gene transfer products to validate biological assay, quantify and interpret results obtained:

The committee discussed how common sense assay design parameters (e.g. understand sources of variability and limit them in system design, use of proper controls, deliberate challenges) should be applied for all assays under development, including potency assays. The Committee also suggested that manufacturers characterize cellular/gene transfer products as best as possible, ensure consistent products and begin to develop potency assays as early in product development as possible.

However, the Committee generally agreed that the state of the science related to novel cellular therapies was not sufficiently developed to allow for a definition of potency in complex molecular entities and it is not possible, at this time, to make specific recommendations on potency assay design and validation for novel cellular

therapies. The Committee discussed how potency assays for other cellular and gene transfer products should be discussed on a case by case basis, rather than in the general context.

Correlation Studies

The Committee was asked to discuss data and study considerations necessary to demonstrate valid correlations:

There was consensus among the Committee that correlation studies are important and the Committee agreed with the FDA's requirement that correlation assays be accurate, precise and sensitive. The Committee did not come to a consensus regarding specific recommendations related to assay design, statistical analysis, controls or limitations of correlation studies.

Some Committee members suggested correlation studies (in products found to be safe) be developed, in the patient, over time/in stages, as more is learned about the product. Other members suggested that assays such as phenotype characterization and flow cytometry could be utilized as potency assays that could correlate with function.

There was consensus among the Committee that products should be well characterized. However, there was no consensus, among the Committee, concerning the need for more stringent standards for correlation and potency studies for complex cellular and gene therapies vs. small molecule (drug) products.

State of the Art Technologies

The Committee was asked to discuss how state of the art technologies such as flow cytometry, genomics, and proteomics may be adapted/implemented for use in product characterization and potency measurement for cellular and gene transfer products:

The Committee suggested micro-array technologies were the most developed of the newer technologies that could potentially be applied to product characterization. The Committee agreed it would be important to identify reference systems and internal controls for micro-array techniques, however one standard reference for all laboratories may not be possible and should not be required.

There was consensus among the Committee that at this time there is not sufficient information on the best use of micro-array technologies in product characterization and therefore the Committee should not make a recommendation for the use of specific micro-array assays for characterizing cellular and gene transfer products.

Following this discussion the meeting was adjourned and reconvened on February 10, 2006.

On February 10, 2006, in open session, the Committee discussed the National Toxicology Program on retroviral vector-mediated mutagenesis.

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Following the call-to-order, Dr. Jesse Goodman, Director, Center for Biologics Evaluation and Research, FDA recognized committee service, with a presentation of plaques to retiring members of the Cellular, Tissue and Gene Therapies Advisory Committee.

The FDA provided an introduction to the National Toxicology Program (NTP) proposed study to assess retroviral vector-mediated insertional mutagenesis and tumorigenesis in a murine model. The presentation also reviewed the rationale for why this was an important study to the FDA. Guest speakers provided 1) data related to a murine model developed to detect side effects caused by insertional mutagenesis of the retroviral vector; and 2) background information on the proposed National Toxicology Program to study retroviral vector-mediated insertional mutagenesis.

Following the guest presentations, the Committee discussed questions from the FDA related to the following issues:

- General scientific approach of the NTP study
- Other models/future studies useful to assess retroviral vector safety
- Possible toxicology models in other cellular or gene therapies that would be useful to study through the NTP
- Use of NTP as a pathway for development of toxicological testing models for other novel therapies

The Committee engaged in an overlapping discussion that broadly touched on the above issues. The Committee was supportive of the proposed NTP study and commended the FDA for bringing the study forward. The Committee stated the proposed NTP study would provide information on the robustness of the model and could provide information related to the safety of vector insulators/enhancers and the risks associated with proviral insertion. Additionally, the study could serve as a critical standard to compare other vectors.

The Committee raised questions about several issues, including the length of time (approximately 2 years) for data collection, the choice of vector constructs for the study (in particular, the committee wanted the study to incorporate a control vector that was completely enhancer deficient) and the rationale for statistical analyses. The Committee was in agreement that the NTP protocol could be useful to study the risks associated with lentiviral vectors, encouraging the initiation of these studies sooner than later. However, they also noted that the specific transduction conditions that are optimal for lentiviral transduction of ex vivo modified hematopoietic stem cells will likely be different than those for gammaretrovirus vectors.

In a brief discussion of the utility of the NTP protocol to study an *in utero* gene transfer model, the Committee felt it is premature to look at *in utero* gene transfer in this system. The Committee felt the NTP pathway could be useful to study systems to kill transduced cells and to compare suicide constructs.

During the Open Public Hearing the Committee received an individual comment regarding the potential of the toxicology program to study other cell populations.

At this time the discussion of the National Toxicology Program for retroviral vector-mediated mutagenesis was completed and the Committee moved to the next topic.

The last topic of the open session was an overview of the research program of the Office of Cellular, Tissue and Gene Therapies, Center for Biologics Evaluation and Research (CBER). The Committee heard presentations related to CBER's research program and research within the Office of Cellular, Tissue and Gene Therapies.

Following the research overviews the open session was adjourned and the Committee reconvened in closed session.

For more detailed information concerning the open session presentations and committee discussion summarized above, please refer to the meeting transcripts available on the FDA website at <http://www.fda.gov/ohrms/dockets>. Please submit all external requests to the FDA Freedom of Information Office.