A publication of
The Williamsburg BioProcessing Foundation

July/August 2003

BioProcessing™ JOURNAL

Advances & Trends In Biological Product Development

Vol. 2 No. 4

www.bioprocessingjournal.com

FDA Educational Partnerships to Improve the Development of Cell and Gene Therapy Products

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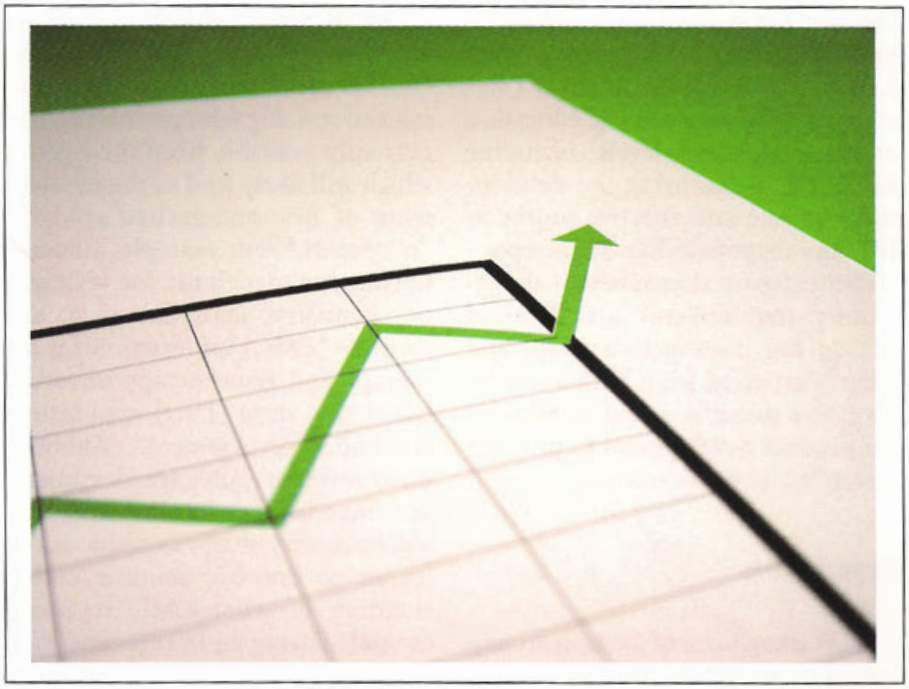

On January 31, 2003, FDA under the leadership of Commissioner Dr. Mark McClellan, issued a report entitled "Improving Innovation in Medical Technology: Beyond 2002".[1] One of the goals described in this report is to "speed potentially important emerging technologies to the market by reducing regulatory uncertainty and increasing the predictability of product development." The technology areas of cell therapy and gene therapy were specifically identified. This article highlights some of the challenges for manufacturers and regulators of these products and describes ongoing efforts at FDA — as well as opportunities to partner with FDA — to improve the product development process for cell therapy and gene therapy products.

Challenges

Cell therapy and gene therapy products are some of the most diverse products regulated by FDA.[2,3] They 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, allogeneic, or xenogeneic) (Table 1), the vector system used, the potential for adventitious agent contamination, the need for aseptic processing, and the inability to "sterilize" the final product if it contains living cells. Distribution of these products can also be a challenge due to stability issues and the potentially 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.

A further regulatory challenge that is often encountered, but uncommon to most other classes of medical products regulated by FDA, is that the majority of cellular and

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Table 1. Cell Therapy and Gene Therapy Files by Cell Source*

Cell Source	Cell Therapy	Gene Therapy
Autologous	42%	31%
Allogeneic	50%	16%
Xenogeneic	8%	0%
Non-cell mediated	0%	53%

* Source: FDA/CBER Biologics IND Management System as of June 1, 2003

gene therapy clinical trials are sponsored by academic-based investigators and are in early phases of product and clinical development (Tables 2 & 3). Consequently, there is a significant need for ongoing education at many different levels, including FDA's role in ensuring the development of safe and effective products. It is the responsibility of the sponsor/investigator to ensure that all regulatory requirements are followed during the investigation trials, and what is expected from both a regulatory and manufacturing standpoint for product development to progress toward potential licensure.

Opportunities

FDA is cognizant of the unique challenges presented by cell therapy and gene therapy products and over the years has developed a multifaceted approach to assist developers of these products. Of particular note is the recent formation of the new Office of Cellular, Tissue, and Gene Therapies (OCTGT) within the Center for Biologics Evaluation and Research (CBER) on October 1, 2002. This Office consolidates the oversight of products containing human cells and tissues, gene therapy, xenotransplantation, therapeutic tumor vaccines, and most living cell-device combination products, within one component of FDA.[4] This should help ensure consistency in review and policy development for these broad technology areas.

To further clarify the flexible regulatory approach FDA has adopted for the manufacture of these products, review staff in the Division of Cell and Gene Therapy (DCGT) within OCTGT are in the process of evaluating and revising relevant information currently available from the Agency, which will likely lead to the development of new and revised guidance documents.[5] For example, guidance documents specifically for reviewers of chemistry, manufacturing, and controls (CMC) information for cell therapy and gene therapy investigational new drug (IND) applications are under development. Although these reviewer guidance documents are intended for internal use, they will be made publicly available as one means to improve sponsor understanding of what CMC reviewers evaluate during an IND review.

New scientific advances, as well as experiences gained from clinical trials, will continue to influence regulatory decision-making in these rapidly evolving technology areas. Review staff from DCGT are committed to working with all stakeholders to ensure these therapies are developed as safely and expediently as possible. As in the past, FDA will continue to discuss the key scientific and regulatory issues affecting the development of these products in public forums, such as relevant FDA advisory committees and the NIH/OBA Recombinant DNA Advisory Committee (RAC).[6]

OCTGT also intends to continue to forge partnerships with appropriate stakeholder groups to facilitate advancement of this field. For example, in the gene therapy arena, manufacture of the Adenoviral Reference Material (ARM) was developed in partnership with FDA, industry, and academia, with the Williamsburg BioProcessing Foundation acting as facilitator.[7,8] OCTGT review staff have participated in educational training sessions held over the past several years in conjunction with meetings of the American Society of Gene Therapy (ASGT), such as the recent Symposium on Non-Clinical Toxicology in Support of Licensure of Gene Therapies workshop held March 13–14 in Washington DC. Similar opportunities are just beginning to be evaluated in the cell therapy arena.

Due to the significant number of academic investigator initiated INDs, in both cell and gene therapy, FDA has begun a number of partnerships with the National Institutes of Health (NIH) to provide an additional avenue for DCGT review staff to interact with specific Institutes within the NIH to help foster the further development of cellular and gene therapy products. Interactions include participation as non-voting members on the steering committees for the National Gene Vector Laboratories and the Islet Cell Resource Centers, as well as a new interagency memorandum of understanding (MOU) between CBER and the National Institute of Neurological Disorders and Stroke (NINDS). The purpose of the MOU is to expedite translation of basic research involving biological therapies to well-designed clinical studies for the treatment of neurological disorders.

Direct outreach to stakeholders by participation in meetings has also been an important mechanism for communicating current FDA thinking on specific product classes, such as gene therapy viral vectors, pancreatic islets, and tumor vaccines, or manufacturing issues, such as comparability.[9–12] To the extent possible, review staff from OCTGT will continue to participate in such important and necessary activities. FDA acknowledges the importance of out-

reach with our stakeholders, however, the current increase in workload and decreased resources have made it difficult for staff to accept all invitations to attend or present at many society and interest group meetings. As an alternative for continued outreach in this time of decreased resources, FDA would like to suggest the possibility of forming more cross-cutting FDA/industry/academic interactions, such as workshops and symposiums, where larger groups of interested parties could meet to discuss, and take a more active role in identifying commonly shared issues or concerns regarding specific product classes. We feel that these interactions would directly further our commonly held goals to make these innovative therapies available to patients.

Summary

Cell therapy and gene therapy are 21st century technology areas holding great promise for the development of a number of effective and innovative therapies for patients. However, there are significant challenges in the manufacturing of safe, consistent, and potent products based on these technologies. Many of these challenges appear to be technical in nature and progress is being made to overcome them. FDA is committed to further clarifying the flexible regulatory approach it has adopted to help overcome some of these challenges, which should ultimately result in increasingly predictable product development. A key aspect of FDA's approach involves indirect communications (such as guidance documents), more direct interactions (such as partnerships with various stakeholder groups), and participation in scientific and regulatory discussions as resources permit. We welcome any additional ideas on how FDA can further improve its ongoing efforts in clarifying the process for product development in these technology areas and in creating the necessary partnerships to move these products forward toward licensure.

Table 2. Cell Therapy and Gene Therapy Files by Sponsor Type*

Sponsor Type	Cell Therapy	Gene Therapy
Academic	78%	56%
Corporate	22%	44%

* Source: FDA/CBER Biologics IND Management System as of June 1, 2003

Table 3. Cell Therapy and Gene Therapy Files by Phase of Clinical Development*

Clinical Phase	Cell Therapy	Gene Therapy
Phase I	58%	64%
Phase II	37%	33%
Phase III	5%	3%
BLA	N=1	N=0
Total Active Files	N=340	N=190

* Source: FDA/CBER Biologics IND Management System as of June 1, 2003

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Representative discussions have included:
- February 27, 2003: Discussion of efficacy data for the use of minimally manipulated hematopoietic stem cells from placental/umbilical cord blood for hematopoietic reconstitution
- October 10, 2002, October 24–26, 2001, and November 16–17, 2000: Multiple discussions related to gene therapy on several topics including product characterization, preclinical models and long-term patient follow-up.
- July 13–14, 2000: Product development issues related to human stem cells as cellular replacement therapies for neurological disorders
- March 20–21, 2000: Issues related to the use of human pancreatic islets for the treatment of diabetes
- January 13, 2000: Xenotransplantation and porcine endogenous retrovirus

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