

Oncology Activity at the
Center for Biologics Evaluation and Research
Food and Drug Administration

Steven Hirschfeld, MD PhD
Office of Cellular, Tissue and Gene Therapy
Center for Biologics Evaluation and Research
FDA

Summary

- Biologic therapy is complex
- Development of biologic therapies requires close integration of product and clinical approaches
- Product and specific clinical development are informed most by programs in related product areas
- CBER has resources and experience to maximize efficiency and safety of biologic therapeutic development
- CBER Oncology is an active program integrated with other programs within the FDA, DHHS and external stakeholders

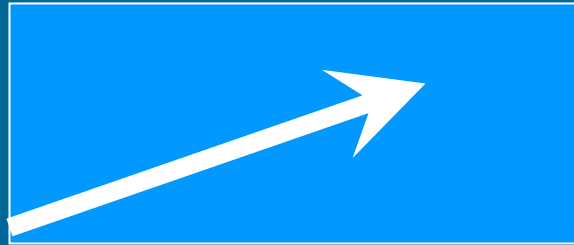
Fundamental Process Difference between Biologics and Drugs

- Most biologics are at least partially manufactured during the process of administration to the patient
 - Example: Personalized tumor vaccine made from tissue from a patient's tumor
 - Example: Patient cells are harvested, transfected with a cloned gene, then returned to patient
- Most drugs are manufactured at a time and place remote from the process of administration to the patient

Product Development

- As clinical development advances, product characterization advances.

Precision of
product
characterization



Stage of development

- Major challenges are determination of purity and potency
- Different from most drugs where product characterization, but not necessarily manufacturing considerations, are completed by early phases of clinical development

Product Complexities

- Product description can have multiple components
 - Example: Modified cells from patient that function as patient specific vaccine
 - Example: Cloned genes that are inserted into vector that are inserted into specific cells isolated from patient
- Product manufacture often has multiple steps
- Product manufacture can be closely integrated with clinical administration

Clinical Development

- Clinical development is closely coordinated to product development
- Paradigms and approaches from other therapeutic areas may not apply due to complexity and need for innovation

Clinical Effects of Biologics

➤ Clinical effects may require multiple activation steps

Example:

- Patient treated to prepare for isolation of cells
- Cells isolated and prepared for modification
- Cells modified in laboratory
- Modified cells infused back into patient

➤ Clinical effects may have multiple events that occur at different times

Example:

- Sequential activation of immune system components coupled with immunologic learning in response to vaccine or cloned gene

Complexities of Regimen

- Concomitant medications may be an integral part of regimen
- Concomitant medications may be used dynamically at different doses or schedules if circumstances change
- Tracking of patients through multiple pathways and study arms is required

Complexities of Trial Design

- Studies will have multiple elements that require monitoring
 - Example:
 - Feasibility and efficiency of isolating cells
 - Clinical effects of any preparatory regimen
 - Feasibility and efficiency of cell modification
 - Efficiency of returning cells to patient
 - Immediate and delayed clinical effects

Complexities of Assessment

- Multiple interim assessments
 - Example (based on previous example):
 - Patients that do not have a response to a preparatory regimen
 - Patients that are unable to have sufficient numbers of relevant cells isolated
 - Cells that are inadequately modified
 - Determining adequacy of returning modified cells to patient
 - Immediate and delayed clinical effects
 - Possibility of need to perform formal analyses to resize or adjust overall sample size at specific points during study

Challenges in Biologics Development

- Need for better understanding of interaction between research and regulations
 - Ideally compliance with regulations and performing scientific and ethical research are congruent
 - Training opportunities in regulatory requirements and perspective are limited
- Need to improve efficiencies in research system
 - Eliminate redundancies and delays
 - Base development on an integrated plan that has flexibility to adapt
- Develop standards for dosing and efficacy assessment
 - Multiple assays and absence of standards impede development
 - Consensus discussions required with scheduled reassessments

CBER Oncology Scope

- Over 600 active INDs in cellular, gene and immunotherapies
- Review staff is board certified hematologists/oncologists
- Oncology program is integrated with general medicine and pediatrics due to similarity of issues with regard to product development and usage but as a separate group due to requirement for disease specific expertise

CBER Oncology Interactions within the FDA

➤ *Weekly*

- Joint rounds between CBER and CDER on Monday AM

➤ *Monthly*

- Oncology Coordinating Committee

➤ *Continual*

- IND specific and issue specific discussions between CBER and CDRH

➤ *Ad hoc*

- Oncology Drugs Advisory Committee
- Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee
- Orphan Drug Grant Review Program CBER & CDER
- Draft Guidance on Oncology Endpoints CBER & CDER

CBER Oncology Interactions with the NCI

➤ *Weekly*

- Clinical Protocol Review on Thursday AM- CBER & CDER

➤ *Monthly*

- NCI-FDA Joint Policy meeting CBER & CDER
- Chemoprevention Working Group CBER & CDER

➤ *Annually*

- Phase I meeting CBER & CDER
- Children's Oncology Group Meetings
- Other Cooperative Group Meetings

Ad hoc

- Interagency Oncology Task Force CBER & CDER
- State of the Science Workshops CBER & CDER
- Small Business Innovation Research (SBIR) CBER & CDER

CBER Oncology Interactions with organizations external to DHHS

➤ *Ad hoc*

- Workshops on disease specific clinical endpoints with professional organizations and stakeholders
- Presentations at national and international meetings of major organizations such as BIO, ASGT, iSBTc, ASCO, AACR, EORTC, patient advocacy groups
- Participation on planning and education committees of ASH, ASCO, AACR, ASPH/O, EORTC

➤ *Planned*

- Workshop on “Efficient Development of Biologics for Cancer Therapy”

FDA Initiatives

- Special Protocol Assessment program

<http://www.fda.gov/cder/guidance/3764fnl.htm>

- FDA-Sponsor meetings with patient representatives

<http://www.fda.gov/oashi/cancer/pconback.html>

- Electronic IND submissions for biologics

<http://www.fda.gov/cber/gdlns/elecgenrev1.htm>

- In partnership with professional organizations
public discussion of clinical trial endpoints

- Training opportunities for fellows and academic investigators at the FDA

Summary

- Biologic therapy is complex
- Development of biologic therapies requires close integration of product and clinical approaches
- Product and specific clinical development are informed most by programs in related product areas
- CBER has resources and experience to maximize efficiency and safety of biologic therapeutic development
- CBER Oncology is an active program integrated with other programs within the FDA, DHHS and external stakeholders