Cell Therapy and FDA Regulation

Celia M.Witten, Ph.D., M.D.
Director, Office of Cellular, Tissue, and Gene Therapies

Mid-Atlantic Bio

October 25, 2007

Bethesda, Maryland

Outline

- OCTGT
- Early Clinical Development
- Critical Paths

Organization

- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cells, gene therapy
  - Office of Cellular, Tissue, and Gene Therapies
  - Office of Vaccines Research and Review
  - Office of Blood Research and Review
- CDER (Center for Drug Evaluation and Research): drugs, some biological products
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CVM
- CFSAN
- NCTR

Office of Cellular, Tissue, and Gene Therapies
Celia M.Witten, Ph.D, M.D.
Stephanie Simek, Ph.D., Office Deputy Director
Richard McFarland, Ph.D, M.D. Associate Director for Policy
Suzanne Epstein, Ph.D., Associate Director for Research
James Reese, Acting Director RPM

Division of Cellular and Gene Therapies
Raj Puri, Ph.D., M.D., Director

Division of Human Tissues
Ruth Solomon, M.D., Director

Division of Clinical Evaluation and Pharmacology/Toxicology
Ashok Batra, M.D.

OCTGT Regulation

- Cellular therapies
- Tumor vaccines/active immunotherapy
- Gene therapies
- Tissue and tissue based products
- Xenotransplantation products
- Combination products
- Devices used for cells/tissues
- Anti-idiotype antibodies

Regulation

- Tissue Rules (Part 1271)
- Biologics (Investigational studies and licensing applications)
- Devices
- Drugs

Early Clinical Development

Cell Therapy Product Characterization

- Morphologic evaluation
- Unique biochemical markers
- Gene and protein expression analysis
- Cellular impurities profile
- Biologic activity/Potency
- Identity: HLA, other unique marker

Product Safety and Efficacy

- Safety Issues:
  - Sterility (bacterial, fungal, mycoplasma)
  - Purity
  - Identity
  - Segregation and tracking
- Efficacy Issues:
  - Potency
  - Stability

Preclinical Evaluation: Cell Therapy and Traditional Biologic Drug Development

- Pharmacologic profiles
- POC
- Dose-response relationship
- Toxicology profile

Cell Therapy Preclinical Assessment: Activity and Safety

- Cell Fate Post Transplant
  - Post transplant survival
  - Cell migration
  - Cell differentiation
  - Cell phenotype expression
  - Anatomic/functional integration into host physiology
  - Tumorigenic/proliferative potential
- And…

Investigational Studies

- Study must be *reasonably safe*
  - Risk vs.benefits
  - First-time-in-humans--most attention of all
  - Consider other trials, indications, similar products ;
- Assess drug exposure; duration of therapy; number of patients exposed; stopping rules and expected/acceptable toxicity; potential benefits; type of patients treated; minimization of risks to subjects; plans for later phases; supporting animal data, clinical data, *in vitro* data, manufacturing issues (e.g., product sterility, lot release data, etc.)

Objectives of Phase 1 Studies for Traditional Drug Development

- Safety/tolerability
- Pharmacokinetics
- Dose selection (MTD)

Objectives of Early Phase Studies for Cell/Gene Therapies may also include information to inform:

- Product characterization
- Product delivery/dosing/safety
- Proof of concept/mechanism of action
- Patient selection (include biomarkers)
- Assessment parameters for toxicity
- Effectiveness parameters (early surrogates and modeling of relationships)
- Timing of assessments
- Duration of observation

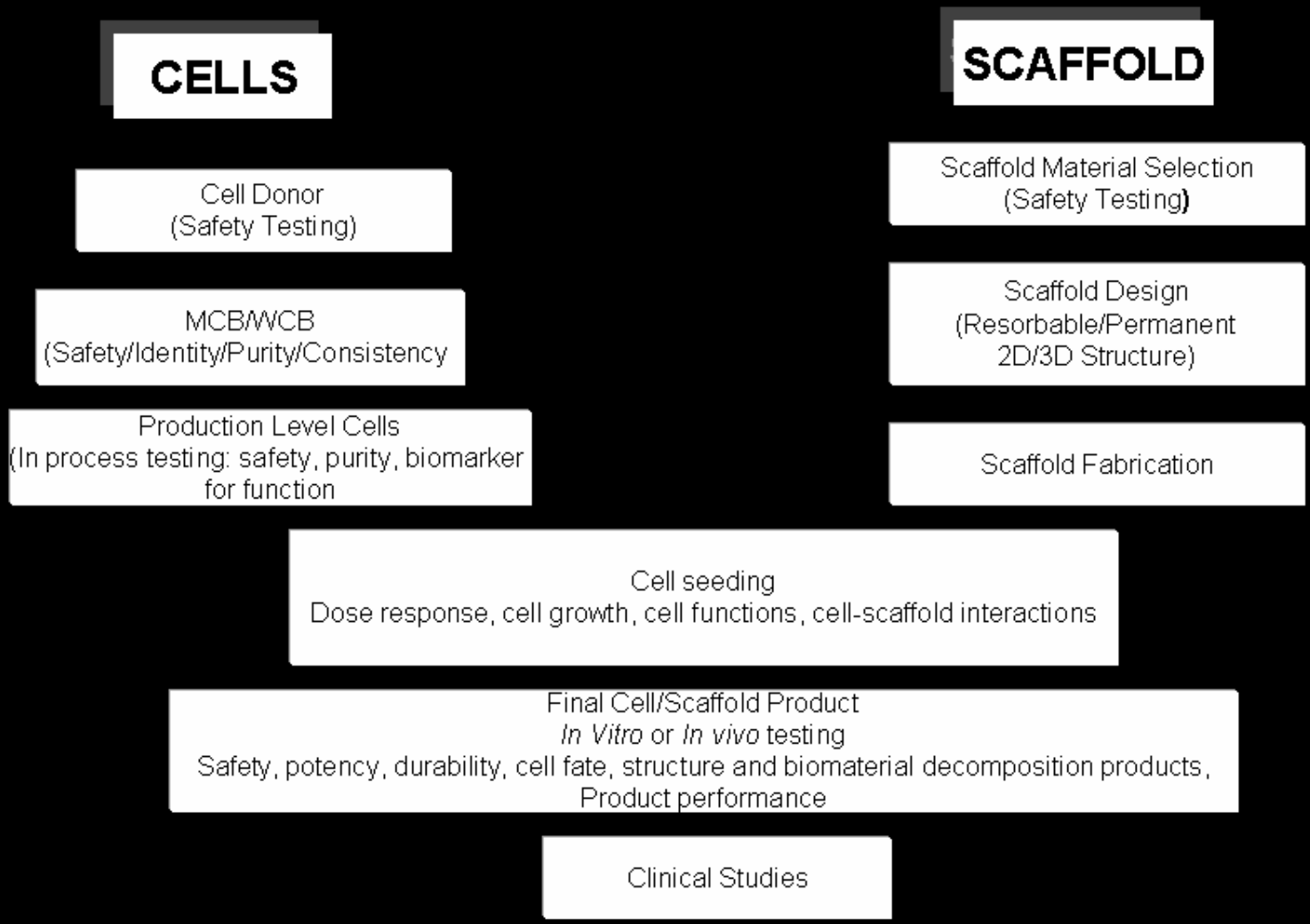
…as well as information to inform the development plan:

- Masking
- Accrual rate
- Effect size
- Decision making criteria for proceeding with development

Important to Define

- Therapeutic product
- Therapeutic target
- Therapeutic goals

Cell Scaffold Products: Characterization and Safety



Basic Scaffold Information

- Scaffold Manufacture
  - Starting material
    - Animal husbandry (if derived from animal tissue)
    - Purity and contaminates (e.g., organic solvents, heavy metals, cross-linking reagents)
  - Manufacturing Processes
  - Sterilization (e.g., bacteria, fungi, viruses, and prions?)

- Scaffold Testing
  - Biocompatibility
  - Scaffold characterization (e.g., thickness, weave , pore size, density, tensile strength, stiffness, burst strength, tear resistance)
  - Final Product Specification (e.g., thickness, pore size, burst strength, residual levels of manufacturing reagents, residual level of heavy metals, pyrogen levels, sterility)

Regenerative Medicine Products

- Guidances for Cellular, Gene Therapies, and Devices
- Leveraging existing guidances to support specific areas of tissue engineered medical products
  - CMC guidances for cellular products
  - General (CT and GT) preclinical guidances
  - Guidances for devices may be applicable to scaffolds
  - Many clinical guidances cross-cut product areas

Upcoming FDA/NIST Public Workshop

In Vitro Analyses of Cell/Scaffold Medical Products

- **December 6-7, 2007**
- **NTSB Conference Center, Washington, DC**
- **http://www.fda.gov/cber/meetings/invitro120607.htm**

The FDA Critical Path Initiative

Established to modernizing the evaluation of safety, efficacy and quality of medical products as they move from product selection and design to mass manufacture

- A key goal is to improve product safety and efficacy and speed products to the patients who need them and the consumers who use them.
- Involves collaborative efforts among government, academia, industry and patient groups.

- FDA Critical Path Goals
- Get more innovative products to patients through development pathways that are efficient and predictable.
- Develop new toolkits that bring scientific advances into the product development process.
- Perform research on tools that remove specific identified obstacles in product development.

Biomarkers Consortium

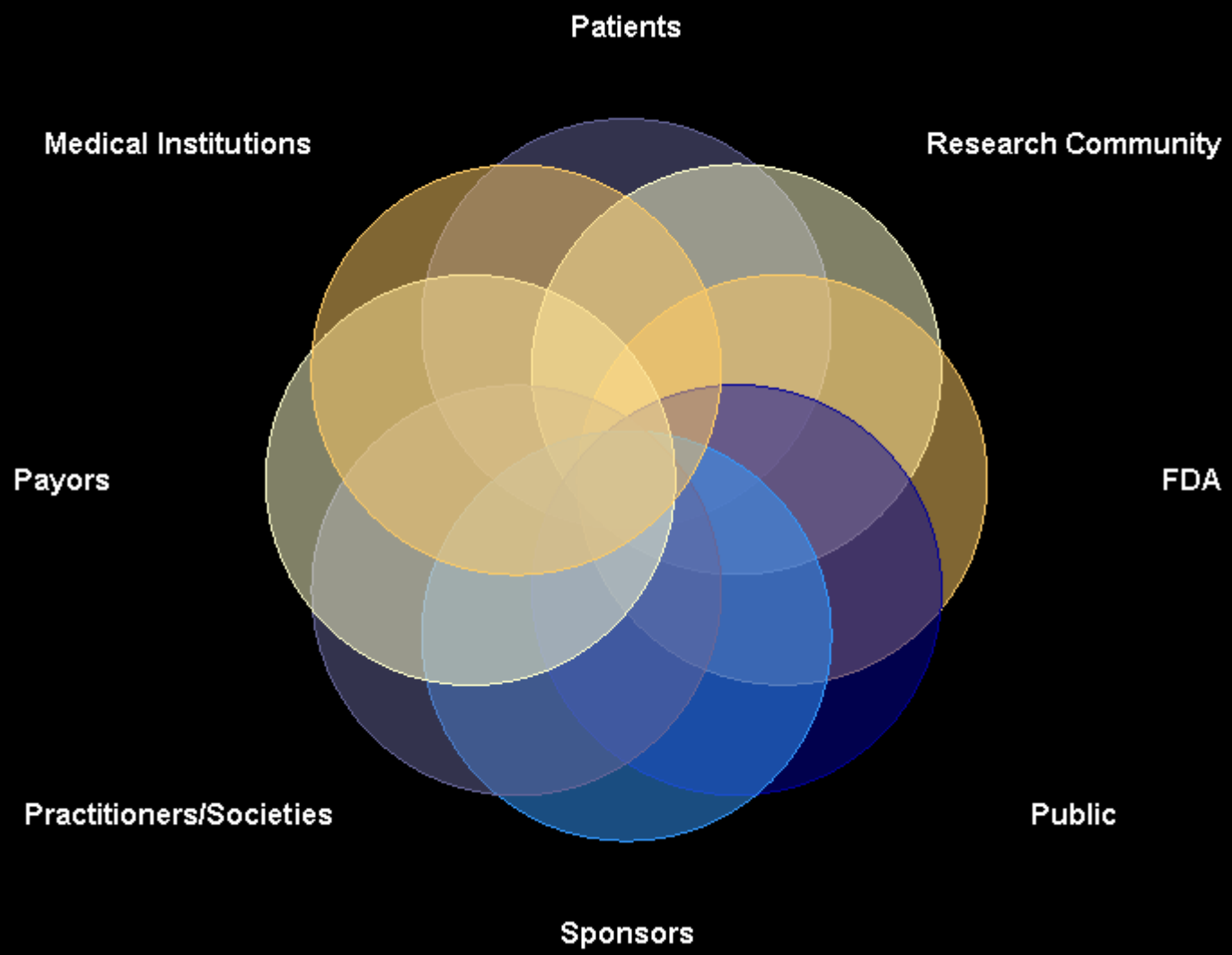
Public-private biomedical research partnership managed by the Foundation for the National Institutes of Health (FNIH).

The Biomarkers Consortium involves government, industry, patient advocacy groups, and other non-profit private sector organizations. In addition to the Foundation for NIH, founding members include:

- NIH
- FDA
- PhRMA
- Centers for Medicare and Medicaid Services (CMS)
- Biotechnology Industry Organization.

Biomarkers Consortium (FNIH)

- Rapidly identify and qualify biomarkers to support basic and translational research and guide clinical practice
- Support the development of safe and effective medicines and treatments.
- Harmonize approaches to identify viable biomarkers
- Verify their individual value, formalize their use in research and regulatory approval.
- www.biomarkersconsortium.org


Patients
Medical Institutions
Research Community
Payors
FDA
Practitioners/Societies
Public
Sponsors

Contact Information

Celia Witten, PH.D., M.D.
Office Director, OCTGT
CBER/FDA
1401 Rockville Pike (HFM 70)
Rockville, MD 20852-1448
301-827-5102