FDA's Perspectives on Quality and Non-clinical Evaluation of Cell/Tissue-based Products

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U.S. Food and Drug Administration (FDA)

FDA protects the public health by assuring the safety, efficacy and security of:

- Human and veterinary drugs,
- Biological products,
- Medical and radiation-emitting devices,
- Foods and cosmetics

FDA Components

- Office of the Commissioner
- **Center for Biologics Evaluation and Research**
- Center for Drug Evaluation and Research
- Center for Devices and Radiological Health
- Center for Veterinary Medicine
- Center for Food Safety and Applied Nutrition
- National Center for Toxicological Research
- Office of Regulatory Affairs
- Office of Combination Products

Center for Biologics Evaluation and Research (CBER)

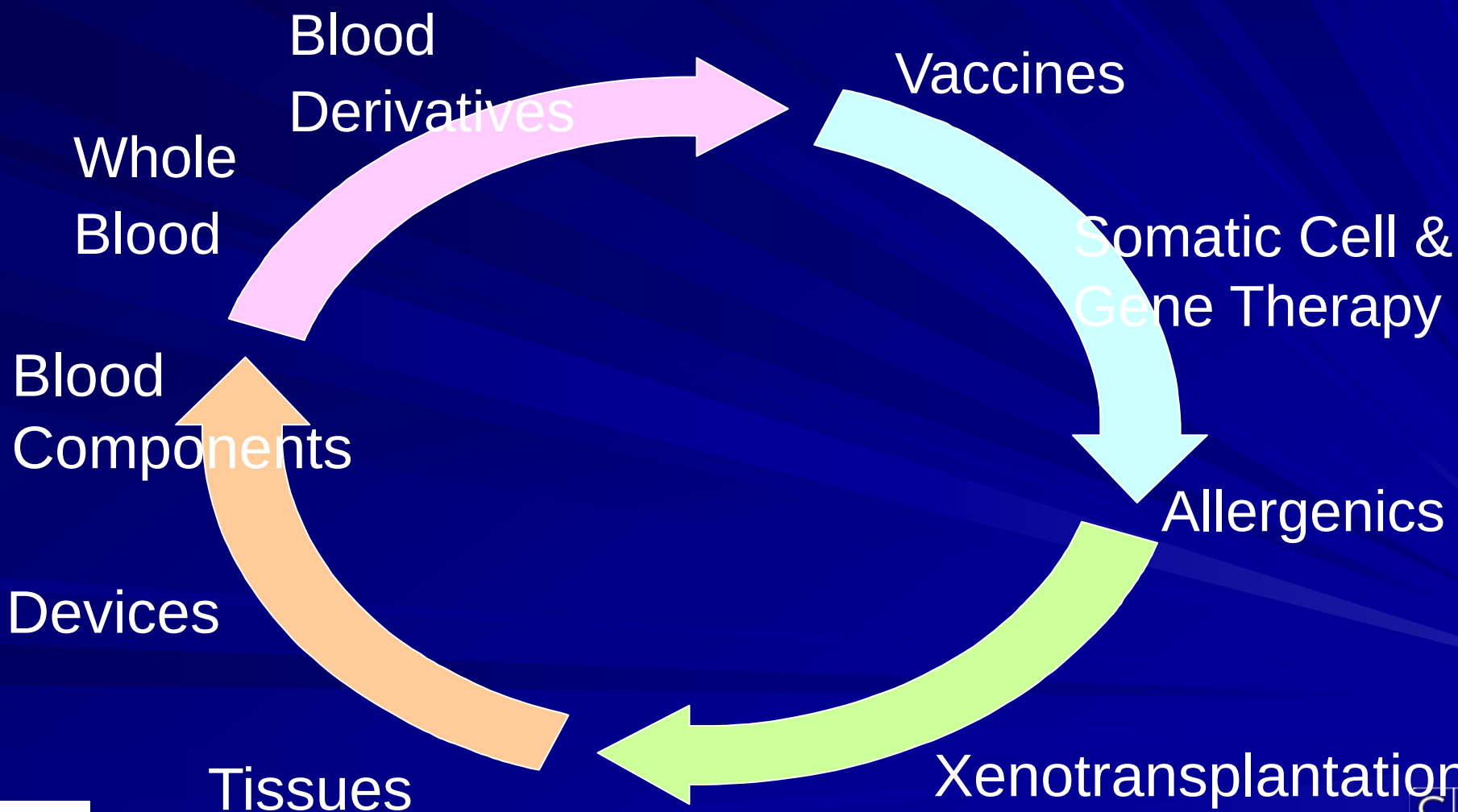
Mission:

Ensure safety, purity, potency and efficacy of biological products.

Biologics – derived from living organisms:

Humans, animals, plants, microorganisms; or created by biotechnology

CBER Products and Research



Biologicals: Unique Issues

The “Process is the Product”

- Complex aseptic manufacturing processes & facilities
- Extensive process controls, standards and assays
- Highest safety standards - given to healthy individuals
  - Vaccines (235 million), Blood (30 M), Tissues (>1 M)
- Market incentives may be weak
  - Income from the sale of all vaccines does not equal income from a single widely prescribed drug

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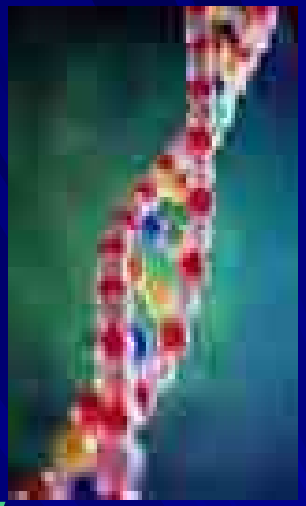
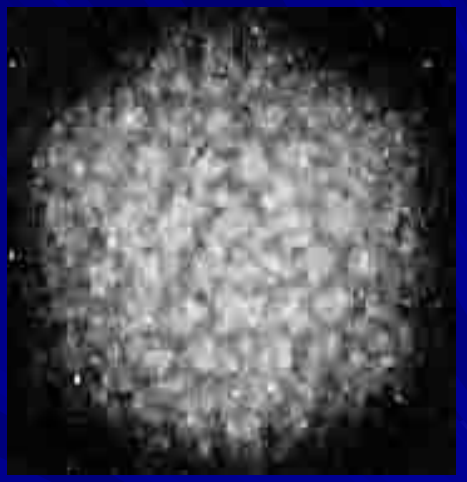
CBER Components

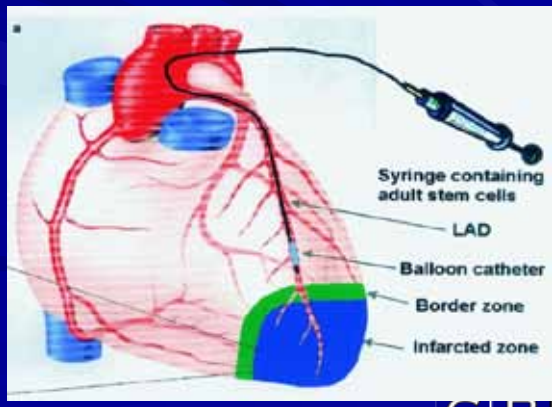


- Office of the Director
- Office of Biostatistics and Epidemiology
- Office of Blood Research and Review
- Office of Cellular, Tissue and Gene Therapies
- Office of Vaccines Research and Review
- Office of Compliance and Biologics Quality
- Office of Communication, Training and Manufacturing Assistance
- Office of Management

Office of Cellular, Tissue and Gene Therapies (OCTGT) Products

- Cellular Therapies
- Cancer Vaccines and Immunotherapy
- Gene Therapies
- Xenotransplantation Products
- Tissues and Tissue-Based Products
- Combination Products
- Devices Used for Cells and Tissues





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Cellular and Tissue-based Products

General Regulatory Approach

Regulation of Cellular and Tissue-Based Products

- A tiered regulatory framework with the level of regulation proportional to the degree of risk
- Provides greater flexibility intended to encourage innovation in the field of cellular therapies
- Risk determines level of regulation
  - ✓ **Lower Risk** – Premarket approval not required; for Control of Communicable Disease the Tissue Regulations Apply: Section 361, PHS Act, 21 CFR Part 1271- *Human Cells, Tissue and Cellular and Tissue-Based Products*
  - ✓ **Higher Risk** – Preapproval Required to demonstrate Safety and Efficacy: Section 351, PHS Act (Biologic); Section 505 Food, Drug and Cosmetic Act (Drug), Investigational New Drug Requirements – 21 CFR Part 312; Investigational Device Exemptions – 21 CFR Part 812.

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Regulatory Framework: Goals

- ✓ Prevent unwitting use of contaminated tissues with the potential for transmitting infectious disease
- ✓ Prevent improper handling or processing that might contaminate or damage tissues
- ✓ Ensure that clinical safety and effectiveness is demonstrated for cells and tissues that are highly processed, used for purposes other than direct replacement, are combined with non-tissue components, or that have systemic effects.

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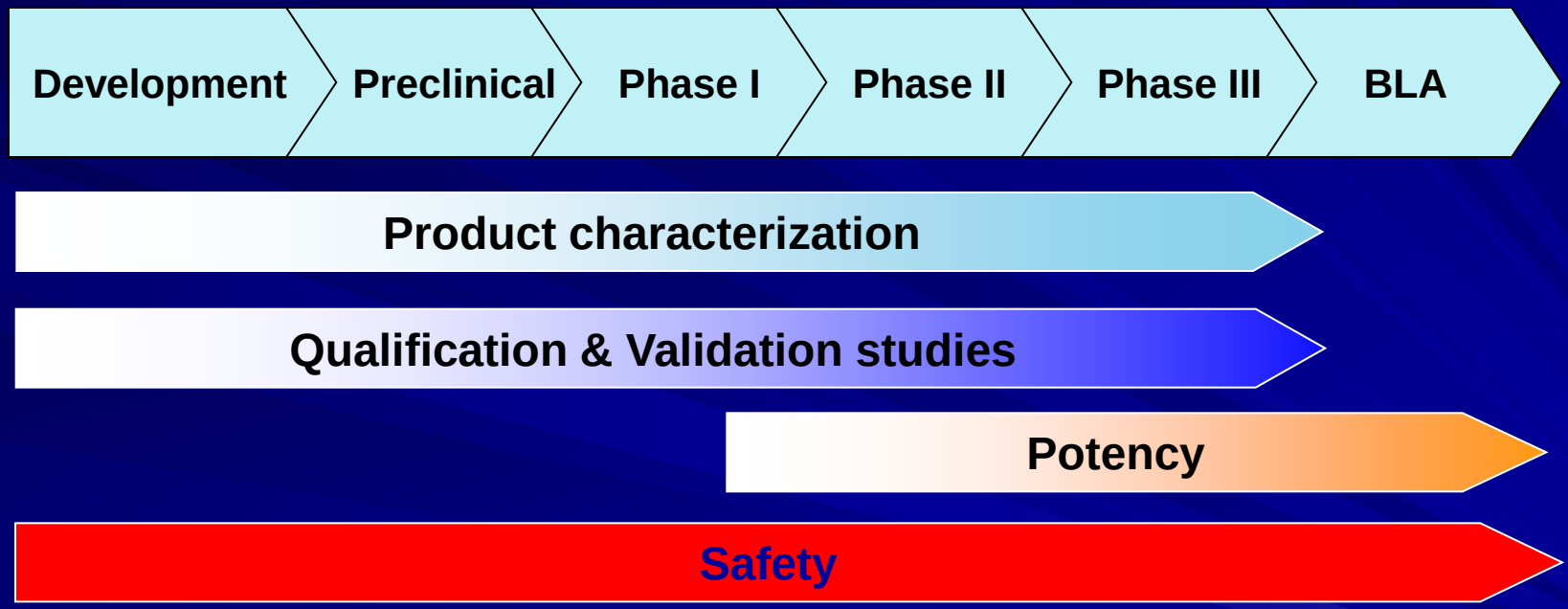
Regulation of Cellular Products

- Federal Food, Drug and Cosmetic Act
- Public Health Service Act, Section 351
  - Premarket approval
  - Demonstration of Safety and Effectiveness
- Public Health Service Act, Section 361
  - Control of infectious disease (21 CFR Part 1271)
- Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, Oct. 14, 1993

Key CMC Issues

Product Development Stage and Review Issues



Stage of product development serves to determine key review issues, with safety being a primary focus during all stages of development/clinical testing.

Regulation of an Evolving Field

- Cell therapy products do not lend themselves to a “one size fits all” concept of product development and regulation
- Regulations set framework of criteria that must be fulfilled: safety, identity, purity, potency, and clinical efficacy
- Flexibility exists in how to fulfill the criteria
- Flexibility is needed for diverse and novel products in evolving fields

Build Quality into the Product

- Requires consistent control of:
  - Cell source; reagents; facility; personnel & equipment
- Validation of:
  - Manufacturing process, aseptic processing, test methods
- Confirm safety and quality of each lot by product testing

Components in Cell Therapy Product Manufacturing

- Starting Cells or Tissues
- Cell Banks (where applicable)
- Raw materials & Reagents (ancillary materials)
  - Materials that are used for cell growth, differentiation, selection, purification, or other critical manufacturing steps, but are not intended to be part of the final product.
- Excipients-
  - intended to be part of the final product

Cell Source

- Allogeneic donors- Donor Eligibility -21 CFR Part 1271 Subpart C
  - Donor testing and screening for relevant communicable diseases
  - Donor screening is medical history interview, physical assessment and medical record review
  - Donors tested using FDA licensed or cleared donor screening tests
- *Autologous donors*
  - Donor testing and screening recommended
- Account for and determine how to control individual donor variability
- Intrinsic safety concerns, based on cell source or cell history

Reagents

- May affect safety, purity, potency, and consistency of the cellular product
- Qualification program
  - Use FDA-approved or clinical grade reagents whenever available
  - Procedures for acceptance of new lots
  - Ensure that reagents are safe and will perform as desired
  - COA review
  - Vendor audits and qualification
  - Additional testing as needed
  - Storage conditions

Manufacturing Process

Goals during development:

- Establish critical manufacturing process controls
- Standardize procedures
- Establish adequate facility and equipment performance standards and monitoring plans
- Develop manufacturing process that will consistently yield a safe, pure, potent product
  - and at the scale you anticipate for commercialization

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Product Testing

- In-process samples from product manufacturing
  - Product and process specific testing
- Final product

- Stability
- Additional characterization
- Shipping Validation

Characterization for Cell-Based Products

- Detect cells with undesired characteristics
  - Minimize undifferentiated and “mis-differientiated” cells
  - Risks of tumorigenicity or ectopic tissue formation
- Ensure that products administered to patients are as safe as possible
  - current limitations in scientific knowledge
- Identify characteristics that predict safety and clinical effectiveness
  - in-process and lot release testing

Guidance Documents for Cell Therapy Product Development

- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy
- Guidance for Industry: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)
- Guidance for Industry - Approaches to Complying with cGMP for manufacture of IND Products Used in Phase 1 Clinical Trials
- Draft Guidance for Industry - Potency Tests for Cellular and Gene Therapy Products
- Draft Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products
- Draft Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage

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Biologics Approval

How is a Biologic Approved?

Product Approval Steps

IND	Goal	Subjects
Phase I	Safety	10-20
Phase II	Dosing/Safety	~20 to 3-400
Phase III	Efficacy/Safety	Large Clinical Trial

BLA – Approval To Market

Post Market Post- Approval Commitments,
Product surveillance
Periodic inspections

Biologics Approval

Be able to show:

- How you derived your Biologic Material
- How you make the Biologic Product
- How it works
- That it works
- That it is safe

Biologics Approval

Know the Regulations

National Archives and Records Administration

code of federal regulations

Biologics Approval

Guidance Resources:

CBER

http://www.fda.gov/cber/guidelines.htm

ICH Guidance

http://www.ich.org/cache/compo/276-254-1.html

Review Steps for a Product

- Pre-filing meeting with review team and sponsor
- Conduct preclinical studies
- File Investigational New Drug (IND) application
- Conduct clinical studies
- File marketing submission (BLA / 510(k) / PMA)
  - Conduct Facility Inspection
  - Conduct lot release activity
- Approve product
- Post Market Surveillance

Investigational New Drug (IND)

- Investigational plan
- Investigator's instructions
- Study protocols
- Manufacturing information
- Pharmacology / Toxicology
- Environmental information
- Previous human experience

http://www.fda.gov/cber/ind/ind.htm

http://www.fda.gov/cber/ind/indpubs.htm

Biologics License Application (BLA)

A request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce

- Labeling
- Manufacturing information
- Clinical trial results
- Pharmacology / Toxicology
- Statistics
- Facility information

Product Approval and Beyond

- Pre-Approval Facility Inspection
- Lot Release (BLA)
- Postmarketing commitments
  - surveillance/adverse event reporting
- Manufacturing changes require prior approval
- Annual reporting; facility inspections

Summary

- CBER Biological Products are diverse and rapidly evolving. They require new regulatory paradigms which are developing rather than established
- Sponsors are encouraged to refer to:
  - Guidance documents and educate themselves
  - Communicate with CBER staff
  - Start solving the problems early: plan ahead
  - Keep good records
- Our scientists facilitate development of, approval of, and access to safe and effective medical products
- Scientists also performs Critical Path research: fill gaps, deal with scientific challenges, figure out what is important

Regulatory Information

References for the Regulatory Process for the Office of Cellular, Tissue, and Gene Therapies (OCTGT)
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

OCTGT Regulatory Questions

- Dr. Patrick Riggins (Branch Chief RPM)
- patrick.riggins@fda.hhs.gov 301-827-5366

General CBER Issues

Office of Communication, Outreach and Development (OCOD)

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CBER Regulatory and Guidance Documents:

http://www.fda.gov/cber/guidelines.htm