



# Cell-Based Medicinal Products for Global Market: FDA Perspectives

CAT-ESGCT Workshop  
ESGCT Annual Meeting, Brighton, UK  
October 27, 2011

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# Outline

- U.S. regulatory framework
- FDA and Office of Cellular, Tissue and Gene Therapies (OCTGT)
- Regulatory approaches to cell and gene therapy products
- Regulatory approaches to biologic-device combination products
- Product development and clinical studies; GMP expectations
- FDA experience with cell and gene therapy products
- FDA-EMA interactions
- FDA/OCTGT resources

# Human Medical Products Regulated in the U.S.

- **Drugs** - Definition: 21 USC 201(g)
- **Biologics** - Definition: 42 USC 351(i)
- **Medical Devices** - Definition: 21 USC 201(h)
- **Combination Products** - Definition: 21 CFR 3.2 (e)(1)

# U.S. Regulatory Framework: 3-Tiered System

- **Statutes** (Laws):

Passed by Congress and signed by the President

- Food, Drug & Cosmetic Act (FD&C Act)
- Public Health Service Act (PHS Act)

- **Regulations** (details of the law):

Written by FDA and approved by the Executive Branch

- 21 CFR (Code of Federal Regulations)

- **Guidance** (FDA's interpretation of the Regulations):

Written and approved within FDA

- Advice non-binding on FDA or sponsor

# U.S. Paradigm for Medical Product Regulation

- **Centralized authority for oversight**
  - FDA oversees the **entire lifecycle** of a medical product from investigational product development to post-marketing surveillance/study
- **Applicable laws with enforcement provisions**
  - Medical products subject to laws and regulations regarding **clinical investigations** and **marketing authorization**
- **Documented policies and guidelines available to public**
  - Federal Register (FR)
  - FDA Guidance Documents
- **Transparency / forum for public discussion**
  - FDA advisory committees; FDA-sponsored public workshops
  - NIH Recombinant DNA Advisory Committee (RAC)

# FDA Organization

- Office of the Commissioner
  - **OCP** (Office of Combination Products)
  - **CBER** (Center for Biologics Evaluation and Research)
    - **OCTGT** (Office of Cellular, Tissue, and Gene Therapies)
    - OBRR (Office of Blood Research and Review)
    - OVRR (Office of Vaccine Research and Review)
    - OCBQ (Office of Compliance and Biologics Quality)
  - **CDER** (Center for Drug Evaluation and Research)
  - **CDRH** (Center for Devices and Radiological Health)
  - CVM (Center for Veterinary Medicine)
  - CFSAN (Center for Food Safety and Applied Nutrition)
  - CTP (Center for Tobacco Products)
  - NCTR (National Center for Toxicological Research)
  - ORA (Office of Regulatory Affairs)

# Examples of OCTGT Products

- **Somatic cell therapies**
  - Stem cells (Hematopoietic, mesenchymal, embryonic), chondrocytes, myoblasts, keratinocytes, pancreatic islets, hepatocytes
- **Gene therapies**
  - Gene modified cells, iPS cells, plasmids, viral vectors, bacterial vectors
- **Cancer vaccines and immunotherapies**
  - Dendritic cells, lymphocyte-based therapies, gene-engineered T cells, tumor tissue-derived products, peptides, proteins
- **Cell-device combination products**
  - Tissue-engineered and regenerative medicine products
- **Devices**
  - Tissue/cell processing/separation, cell selection, cell delivery, companion diagnostics
- **Tissues and Tissue-based products**
- **Xenotransplantation products**

# Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps)

- **Definition:** Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient (21 CFR 1271.3 d).
- **Examples of HCT/Ps**
  - Musculoskeletal tissue, skin, ocular tissue, human heart valves; vascular graft, dura mater, reproductive tissue/cells,
  - Stem/progenitor cells; somatic cells
  - Cells transduced with gene therapy vectors
  - Combination products (e.g., cells or tissue + device)
- **Not HCT/Ps**
  - Minimally manipulated unrelated donor bone marrow - HRSA
  - Vascularized human organs – overseen by HRSA
  - Blood vessels recovered with organs and used for organ transplantation only
  - Blood and blood products - separate regulatory pathway



# HCT/Ps – Two Regulatory Tiers

Risk determines the level of regulation:

- **Tissue** (“361 HCT/P”) – *lower risk*
  - Section 361 of PHS Act
  - Premarket review and approval not required; Product regulated solely under Tissue Regulations to control communicable disease (21 CFR 1271)
  - Establishment registration and product listing required (21 CFR 1271 -Subpart B)
- **Therapeutic** (“351 HCT/P”) – *higher risk*
  - Sections 351 & 361 of PHS Act, FD&C Act
  - Product regulated under Tissue Regulations and premarket review requirements (21 CFR Parts 1271, 600, 200, 312, 812(if device))
  - Regulatory path: can be **BIOLOGIC** or **DEVICE**

# Single Entity Products

	361 HCT/P	351 HCT/P	
	Tissue	Biologic Therapeutics	Device
Applicable Laws	361 PHS Act	361 PHS Act, 351 PHS Act, FD&C Act	FD&C Act
Applicable Regulations	21 CFR 1271	21 CFR 1271, 21 CFR 600's, 21 CFR 200's 21 CFR 300's	21 CFR 800's
Marketing Pathway	Premarket review not required	BLA	PMA, 510(k), HDE

# Combination Products

- A product composed of different categories of regulated articles:
  - Device-biologic, biologic-drug, drug-device, biologic-drug-device (not biologic-biologic, etc)
- Both components are:
  - intended for use together
  - **required to mediate the intended therapeutic effect**
- Can be:
  - Physically or chemically combined
  - Co-packaged; or packaged separately but cross-labeled

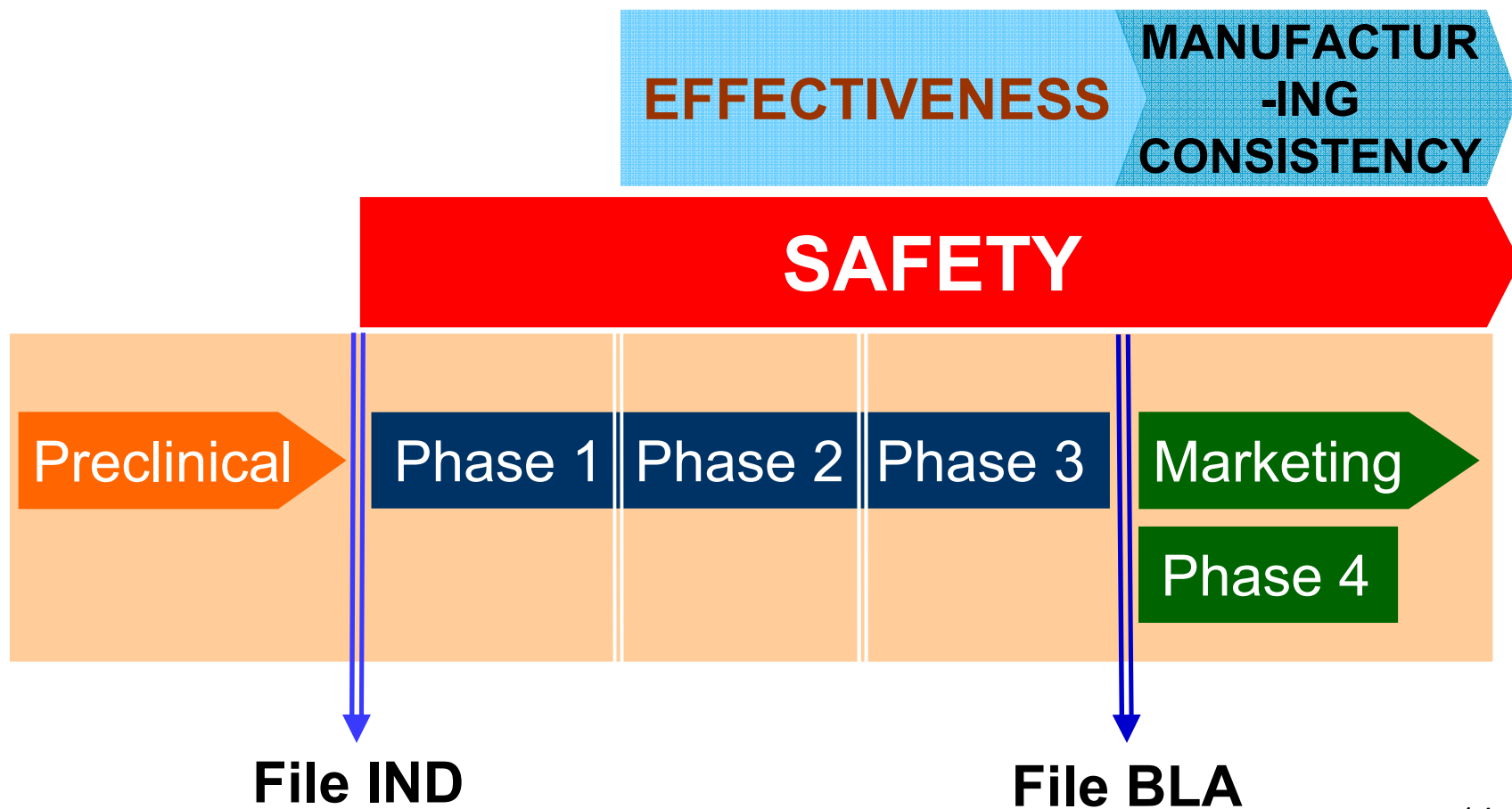
## Examples of Biologic-Device Combination Products

- **Tissue-engineered and regenerative medicine products (TEMPs): cell-scaffold/matrix constructs**
  - **For tissue regeneration, repair and replacement:**  
Orthopedic, cardiovascular, wound healing, musculoskeletal, ophthalmologic, osteogenic ..... indications
- **Bioartificial metabolic support system:**
  - **Hepatic, urinary, renal ..... indications**
- **Cells (and gene) + delivery device (catheters, injection/spray devices, etc):**
  - **Cardiovascular, orthopedic, musculoskeletal, wound healing..... indications**

# Determining Lead Review Center for Combination Products

- **Publically Available Resources**
  - <http://www.fda.gov/CombinationProducts/default.htm>
- **Informal Jurisdictional Inquiries**
  - Center Jurisdictional Officers
- **Office of Combination Products (OCP)**
  - OCP Jurisdictional Updates
  - Request for Designation (RFD): lead review center designated based on primary mode of action determination, inter-center agreements, precedence

# Focus of IND/BLA & IDE/PMA Review



# What is needed to begin a clinical trial ?

- Before filing the IND:
  - Support the safety of clinical trials through **preclinical studies**
  - Provide evidence to support human dosing
  - Provide information to support scientific rationale
  - Provide well developed & controlled manufacturing scheme
  - Provide data on product characterization
  - Provide data to support specifications for product quality control and release

# Pre-Clinical Studies

- Scientific basis for conducting clinical trial
- Data to recommend initial safe dose & dose escalation scheme in humans
- Proof of Concept Studies in relevant animal models
- Toxicology Studies in relevant animal species
  - Identify, characterize, quantify the potential local and systemic toxicities



# Clinical Studies: Early Phase Considerations

- Optimal dose and administration
  - Starting dose level/dose escalation scheme
  - Route of administration
  - Dose schedule
- Define appropriate patient population
- Staggering of dose escalation
- Safety Monitoring plans
- Safety Reporting requirements

# Chemistry, Manufacturing, & Controls

- CMC = product manufacturing and testing
- How do you make the product?
  - Processing and manufacturing
- What do you use to make the product?
  - Cell or tissue source
  - Vector or genetically modified cell if gene therapy
  - Reagents and components
  - Manufacturing equipment
- Product Safety testing: **sterility, endotoxin, mycoplasma**
- Product Quality testing: **viability, identity, purity, stability, potency**
- Other controls: product container labels, tracking
- Product comparability

## Expectations for cGMP

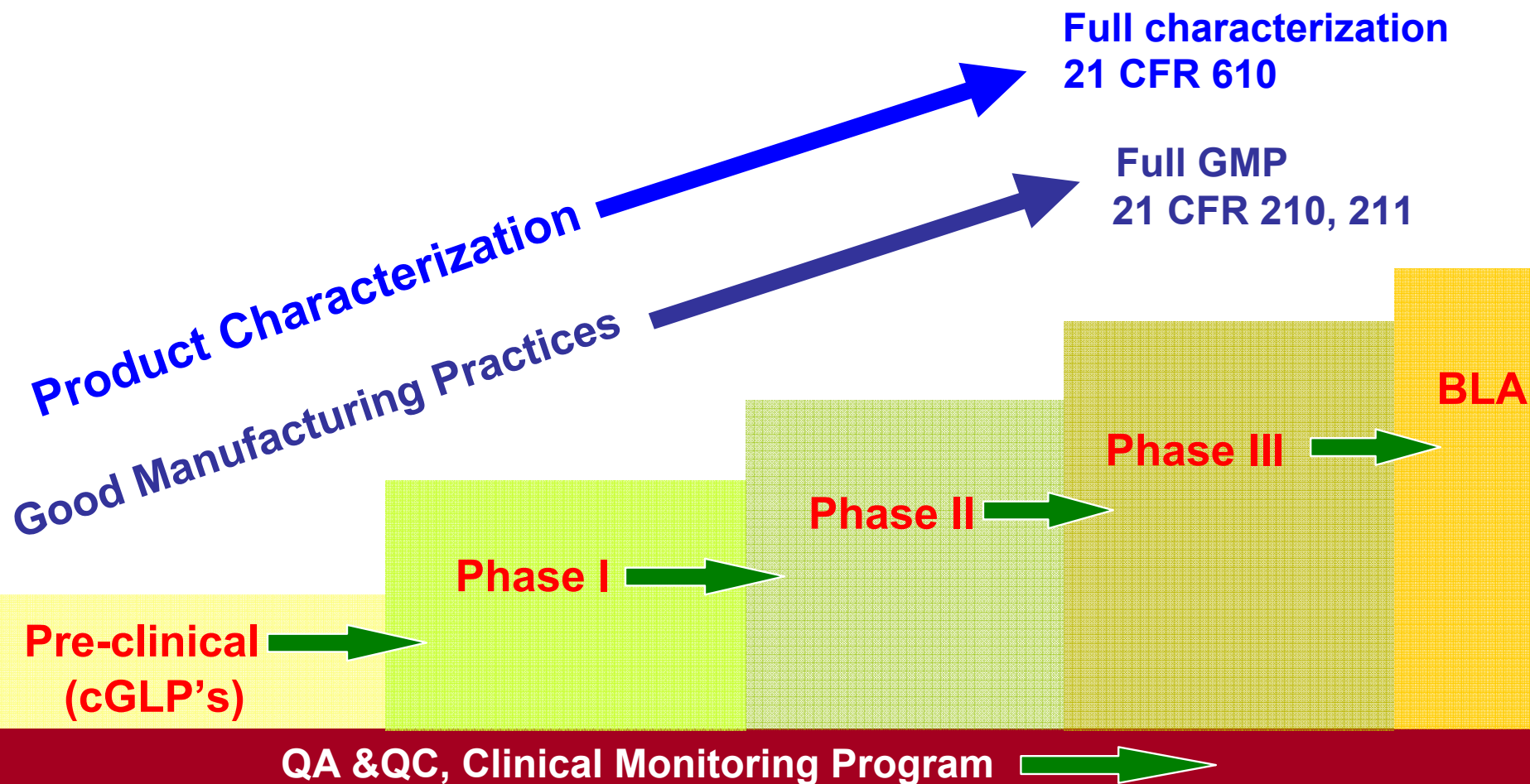
- The “c” means **current**
- GMPs are **minimal standards**
- GMPs cover manufacturing, controls, testing and documentation. Key elements:
  - Facility designed to control operations
  - Adequate documentation/records
  - Production and process controls
  - Quality control/assurance
  - Validation
  - Equipment calibrated/qualified
  - Personnel training & certification
  - Environmental monitoring

# FDA cGMP Guidance

- Guidance for industry cGMP Phase 1 investigational drugs (2008):
  - Recognizes that some controls and the extent of controls differ between investigational and commercial manufacturing, as well as phases of clinical studies
  - Articulates the expectation that there will be greater control over the process through the various IND phases

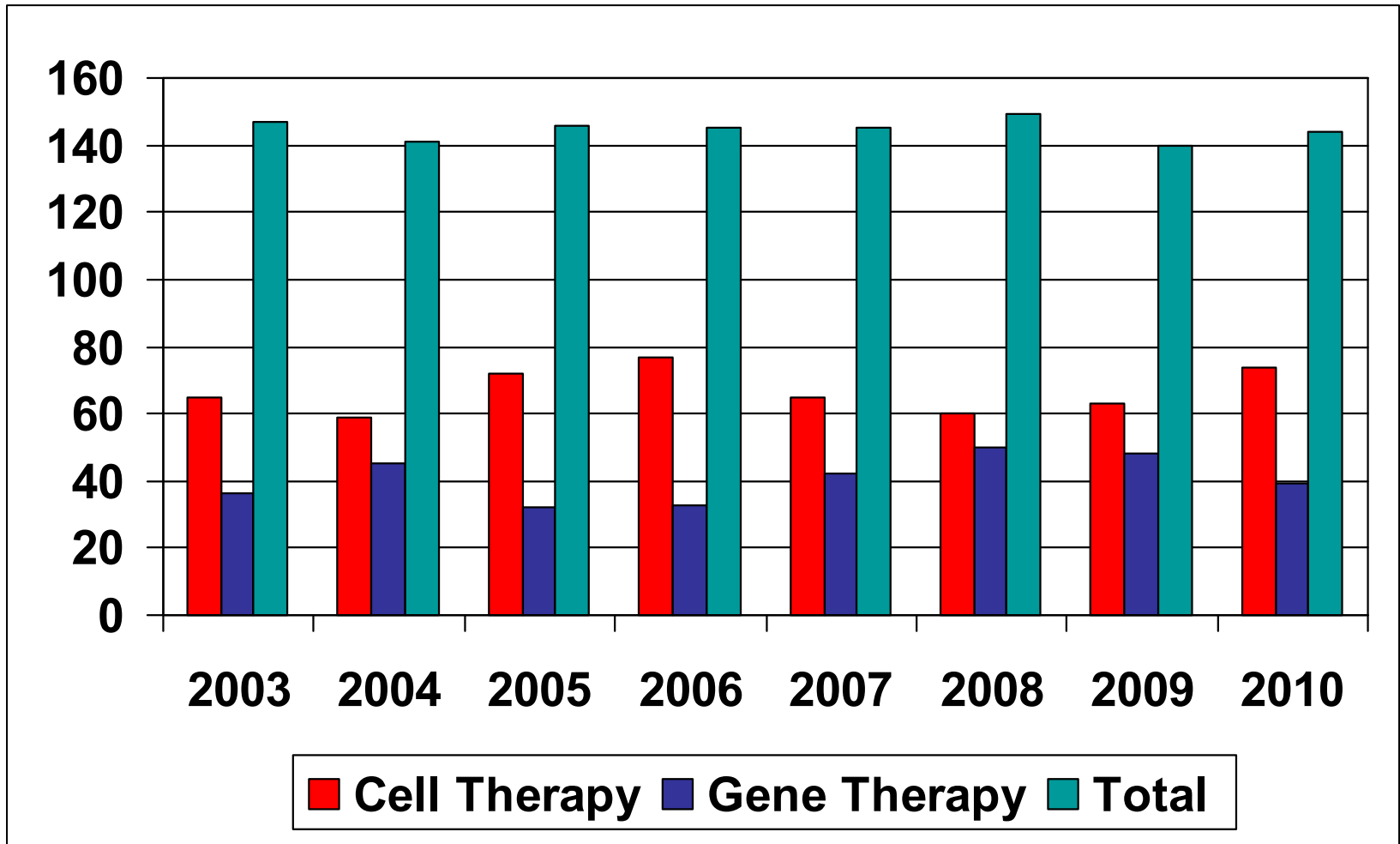


# Step-wise Approach to Regulatory Requirements





## New Submissions to FDA: Investigational CT & GT Products



## Approved Cellular Products in the U.S.

Carticel®	Genzyme Biosurgery	BLA
Provenge® (Sipuleucel-T)	Dendreon	BLA
Laviv™ (Azficel-T)	Fibrocell Technologies	BLA
Apligraf (Graftskin)	Organogenesis	PMA
OrCel	Ortec	PMA
Dermagraft	Advanced BioHealing	PMA
Dermagraft-TC	Advanced Tissue Science	PMA
Epicel	Genzyme	PMA
Integra Artificial Skin	Integra LifeSciences Corp.	PMA

(October 26, 2011)

**BLA:** Biologic License Application; **PMA:** Premarket Approval (device)

# FDA-EMA Interactions

- Formal cooperation and confidentiality arrangement between FDA and EMA for pharmaceuticals (2003-extended indefinitely)
- FDA-EMA **Parallel Scientific Advice** including ATMP
- **ATMP Cluster** initiated in 2008; bi-monthly meetings to share thinking on regulatory approaches, both general and specific issues; EMA/CAT and FDA/OCTGT lead
- Other Clusters
  - Pediatrics, Oncology, etc
- FDA-EMA **exchange fellowship program** on ATMP areas



# CBER/OCTGT Regulatory Resources

- General information for OCTGT and related regulatory references

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm>

- Guidance Documents for Cell and Gene Therapies

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm>

- Regulatory Questions

Contact the Regulatory Management Staff  
 CBEROCTGTRMS@fda.hhs.gov  
 or Patrick.Riggins@fda.hhs.gov  
 or by calling (301) 827-6536

# OCTGT Learn Webinar Series

<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>

- Introduction and Scope of OCTGT
- IND Basics in OCTGT
- Sponsor Meetings with OCTGT
- “361” Human Cells, Tissues, & Cellular and Tissue Based Products
- The Chemistry, Manufacturing and Controls (CMC) Section of a Gene Therapy IND
- Advanced Topics: Successful Development of Quality Cell and Gene Therapy Products
- Cellular Therapy Products
- Preclinical Considerations for Products Regulated in OCTGT





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# FDA White Oak Campus







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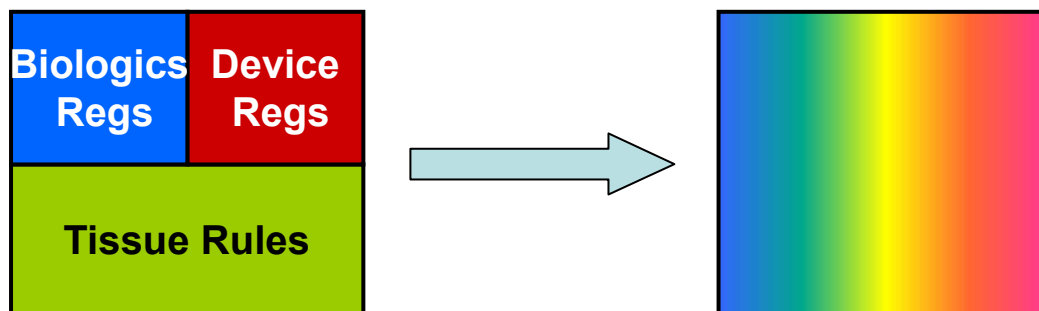
**E-mail: [steven.oh@fda.hhs.gov](mailto:steven.oh@fda.hhs.gov)**

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# Regulatory Paradigm for Biologic-Device Combination Products

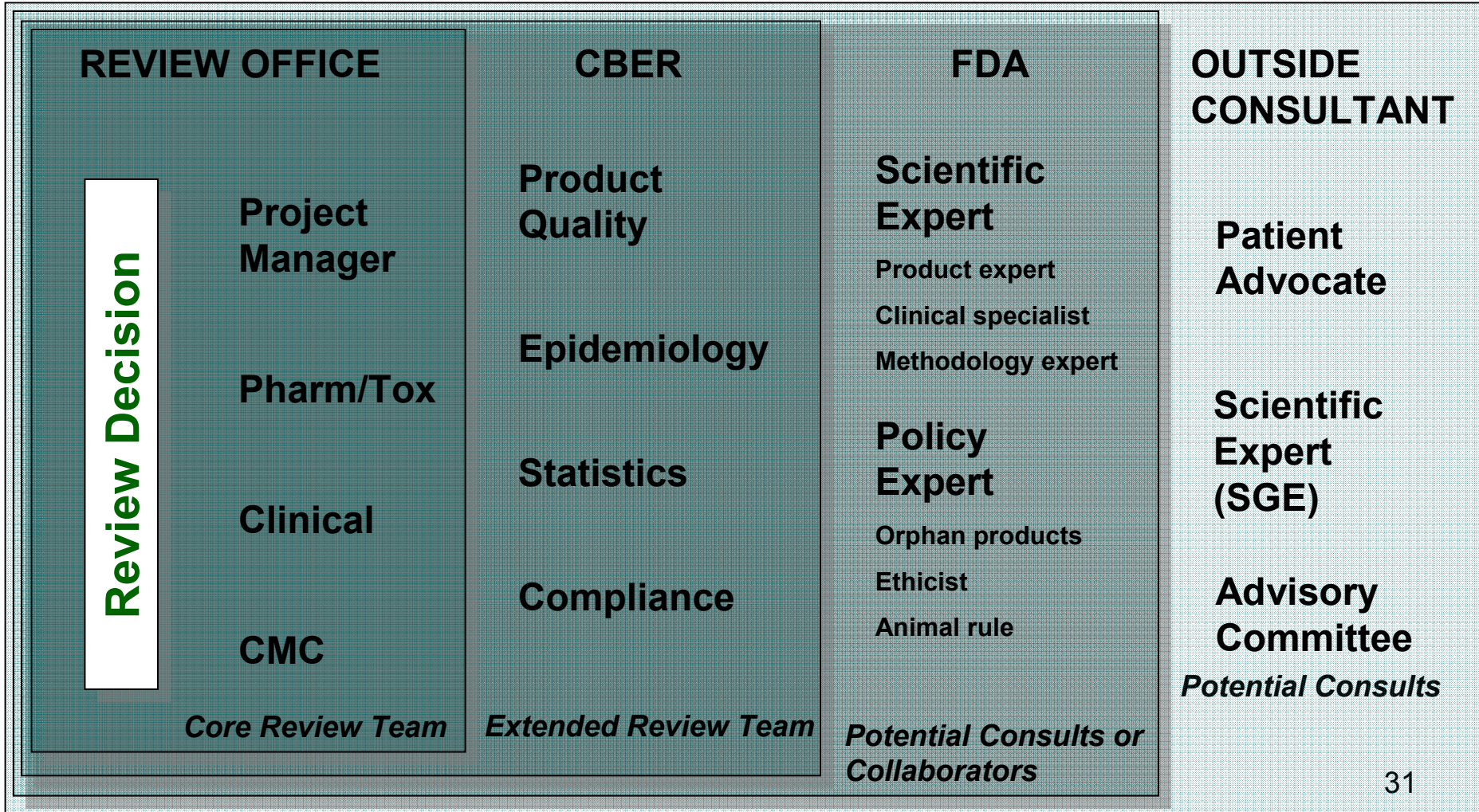
- Flexible quality management regulatory framework
  - **Risk-based approach:** Allows manufacturers to select cGMP or QSR (Quality System Regulations –device regs), provided their system incorporates select, key provisions from the regulations pertaining to the other part of their comb product –Proposed Rule (2009): cGMP Requirements for Combination Products



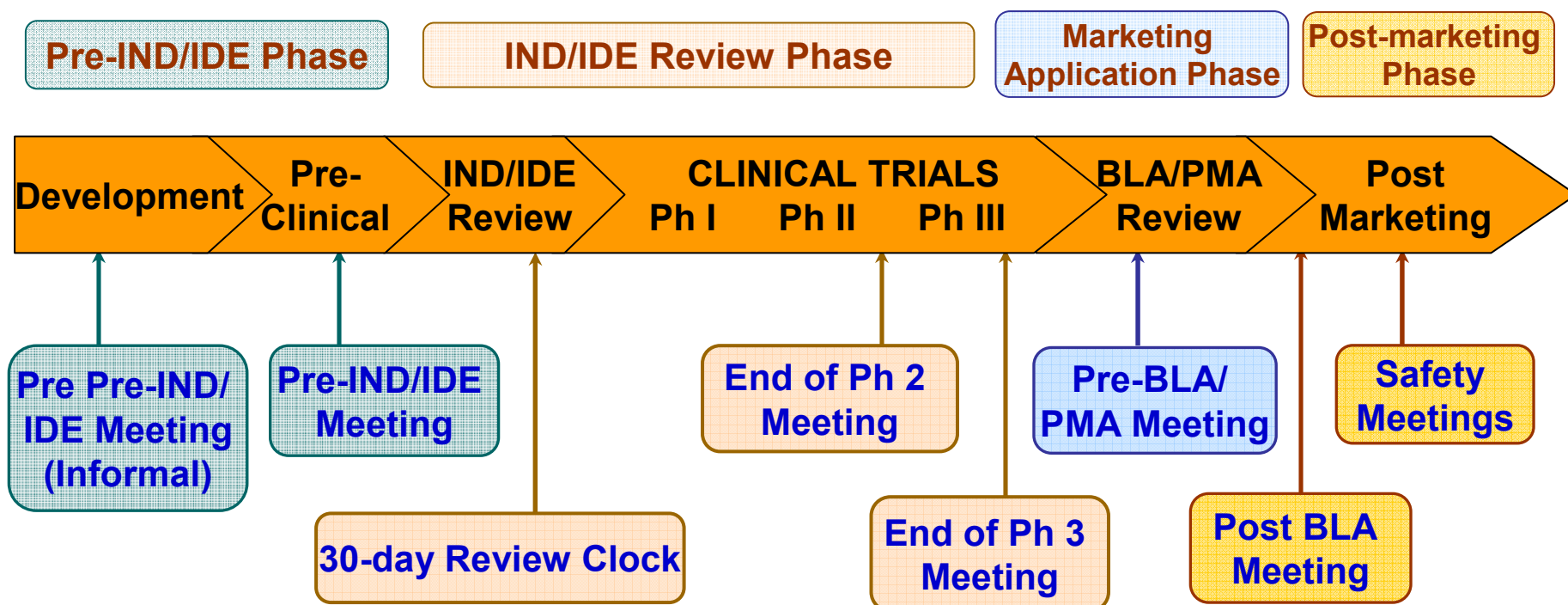
- Comb products produced as a single entity or co-packaged: Both GMP and QSR applicable as necessary during and after combining the constituent parts



# FDA/CBER Review Team



# Interactions with FDA Throughout the Product Lifecycle



- Provide advice to specific queries (face-to-face or by teleconference)
- Written minutes for formal meetings; no fees



# Total Active Files (IND, IDE, MF) in FDA/OCTGT

