



US FDA Regulatory Framework for Cellular Therapy Products

Global Regulatory Perspectives Workshop
22 April 2013

Kimberly Benton, Ph.D.

Deputy Director, Division of Cellular and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies
Center for Biologics Evaluation and Research
US Food and Drug Administration

FDA Mission Statement

- The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

FDA Organization

- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cellular therapies, gene therapies
- CDER (Center for Drug Evaluation and Research): drugs, some biological products
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CFSAN
- CTP
- CVM
- NCTR
- OC
- ORA

CBER Organization

- **CBER regulates:** vaccines, blood and blood products, human tissue/tissue products for transplantation, cellular therapies, gene therapies
 - **Office of Cellular, Tissue, and Gene Therapies**
 - Office of Vaccines Research and Review
 - Office of Blood Research and Review
 - Office of Compliance and Biologics Quality
 - Office of Biostatistics and Epidemiology
 - Office of Communication, Outreach, and Development
 - Office of Management
 - Office of Information Technology

} Product
Offices

Examples of OCTGT Products

- Stem cell and stem cell-derived products
 - Hematopoietic, mesenchymal, cord blood, embryonic, iPSc, etc
- Somatic cell therapies
 - Pancreatic islets, chondrocytes, myoblasts, keratinocytes, hepatocytes,
- Gene therapies
 - Genetically modified cells
 - Plasmids, viral vectors, bacterial vectors
- Therapeutic vaccines and other antigen-specific active immunotherapies
 - Cancer vaccines and immunotherapies, such as dendritic cells, lymphocyte-based therapies, cancer cell-based therapies, peptides, proteins
 - Non-infectious disease therapeutic vaccines, such as peptides, proteins, small molecules
- Devices and combination products
 - Devices with a cellular component
 - Selected devices for the manufacture and/or delivery of a biologic product at the point of care

FDA Paradigm for Medical Product Regulation

- Centralized (federal) 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 presentations at public meetings

Regulatory Framework

- 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

FDA Regulates Human Medical Products

- Drugs - Definition: 21 USC 201(g)
- Devices - Definition: 21 USC 201(h)
- Biologics* - Definition: 42 USC 351(i)

* Includes human cells, tissues, and cellular and tissue-based products (**HCT/Ps**): *Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.*

21 CFR 1271.3(d)

Two General Classes of FDA-Regulated Medical Products

- No Premarket Review
 - Some Human Tissues - “361 HCT/Ps”
 - Some Devices (exempt 510(k))
 - Some Drugs (monograph)

 - Premarket Review/notification
 - 510(K) Devices (non-exempt)
 - PMA Devices
 - BLA- Biologic Drugs
 - NDA- Drugs
- } “351 HCT/Ps”

Regulatory Framework for HCT/Ps

-21 CFR Part 1271-

- The three rules of 21 CFR Part 1271 form the platform for regulation of all human cells, tissues, and cellular and tissue-based products (HCT/Ps)
- For certain HCT/Ps (“361 HCT/Ps”), the tissue regulations comprise the sole regulatory requirements
- For HCT/Ps regulated as drugs, devices, and/or biological products, the tissue regulations supplement other requirements (GMP/QSR, 600s, etc., as applicable)

The “Tissue Rules”

(21 CFR 1271, Effective May 25, 2005)

Tissue Rule	Issues Addressed
Establishment Registration and Listing	Applicability: types and uses of products that will be regulated by these rules; requirements for registering and listing products
Donor Eligibility	Requirements for donor screening and testing for “relevant communicable disease agents and diseases”
Current Good Tissue Practice (CGTP)	Manufacturing to ensure that HCT/Ps do not contain communicable disease agents; reporting; inspections

What is, and what is not, an HCT/P

- Regulated as HCT/Ps
 - Musculoskeletal tissue
 - Skin
 - Ocular tissue
 - Human heart valves; vascular graft
 - Dura mater
 - Reproductive tissue/cells
 - Hematopoietic stem/progenitor cells; other cellular therapies
 - Combination products containing cells or tissues

- Not regulated as HCT/Ps
 - Vascularized human organs
 - Blood and blood components
 - Minimally manipulated bone marrow for homologous use
 - Blood vessels recovered with organs and used for organ transplantation only
 - Autologous cells recovered and implanted during the same surgical procedure
 - Reproductive cells implanted into the partner of the donor

Regulatory Categories for HCT/Ps -1-

- **Tissue- “361 HCT/P”**

- PHSA 361 and 21 CFR 1271 apply
- Focus is on control of communicable disease
- No premarket review required if ALL of the following criteria are met (21 CFR 1271.10):
 - Minimally manipulated, and
 - Intended for homologous use, and
 - Not combined with another article, and
 - Either does not have a systemic effect or require living cells; or has a systemic effect and is for autologous use, for 1st or 2nd degree related recipients, or for reproductive use

Homologous Use

21 CFR 1271.3(c)

- repair, replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic functions in the recipient as in the donor.

Minimal Manipulation

21 CFR 1271.3 (f)

- (a) For structural tissue –
processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, and replacement.
- (b) For cells or non-structural tissue –
processing that does not alter the relevant biological characteristics of cells or tissues

Regulatory Categories for HCT/Ps -2-

- “351 HCT/P”

- Does not meet one or more of the criteria 21 CFR 1271.10 to be “kicked down” to 361 HCT/P
- Premarket review required
- Regulatory path of **Biologic** or **Device** according to which definition is applicable
 - Note: Includes autologous products that are either
 - More than minimally manipulated
 - Not for homologous use
 - Combined with another article

“351” Cell Therapy Biologic Products

- Fit regulatory definitions of the following:
 - Human cells, tissues, or cellular and tissue based products (HCT/P) (21 CFR 1271.3(d))
 - Biologics (PHS Act)
 - Drugs (FDC Act)
 - Somatic Cellular Therapy Product (1993 FR)
 - & Gene Therapy Product, when genetic material is transferred to cells ex vivo

Applicable Regulations for Cellular Therapy Biologic Products

- 21 CFR 1271 Subparts A-D – HCT/Ps
- 21 CFR 312 - Investigational New Drug (IND) Application
- 21 CFR 210/211 - Good Manufacturing Practice
- 21 CFR 50 - Protection of human subjects
- 21 CFR 56 - Institutional Review Boards
- 21 CFR 201 - Labeling
- 21 CFR 202 - Advertising
- 21 CFR 600 - Biological Products; General
- 21 CFR 601 - Licensing
- 21 CFR 610 - General Biologics Standards

FDA Review of Safety & Effectiveness

- FDA reviews both investigational and marketing applications
 - Regardless of funding source (academic or industry)
- FDA review is product-based
 - Parallels prudent product development
 - Early interactions with sponsors facilitate effective product development
 - Detailed manufacturing information is needed during product development
 - Preclinical studies designed to support the use of specific products
 - Clinical trial design supported by manufacturing, preclinical data

Authority for Review of Investigational Products

- A new biologic, drug, or device may not be entered into interstate commerce unless:
 - It is approved by the FDA as safe and effective (biological license application [BLA], new drug application [NDA], pre-market approval [PMA], or other marketing approval)
- OR...
 - An Investigation New Drug exemption (IND) is in effect (exempting the study from the premarketing approval requirements that are otherwise applicable)

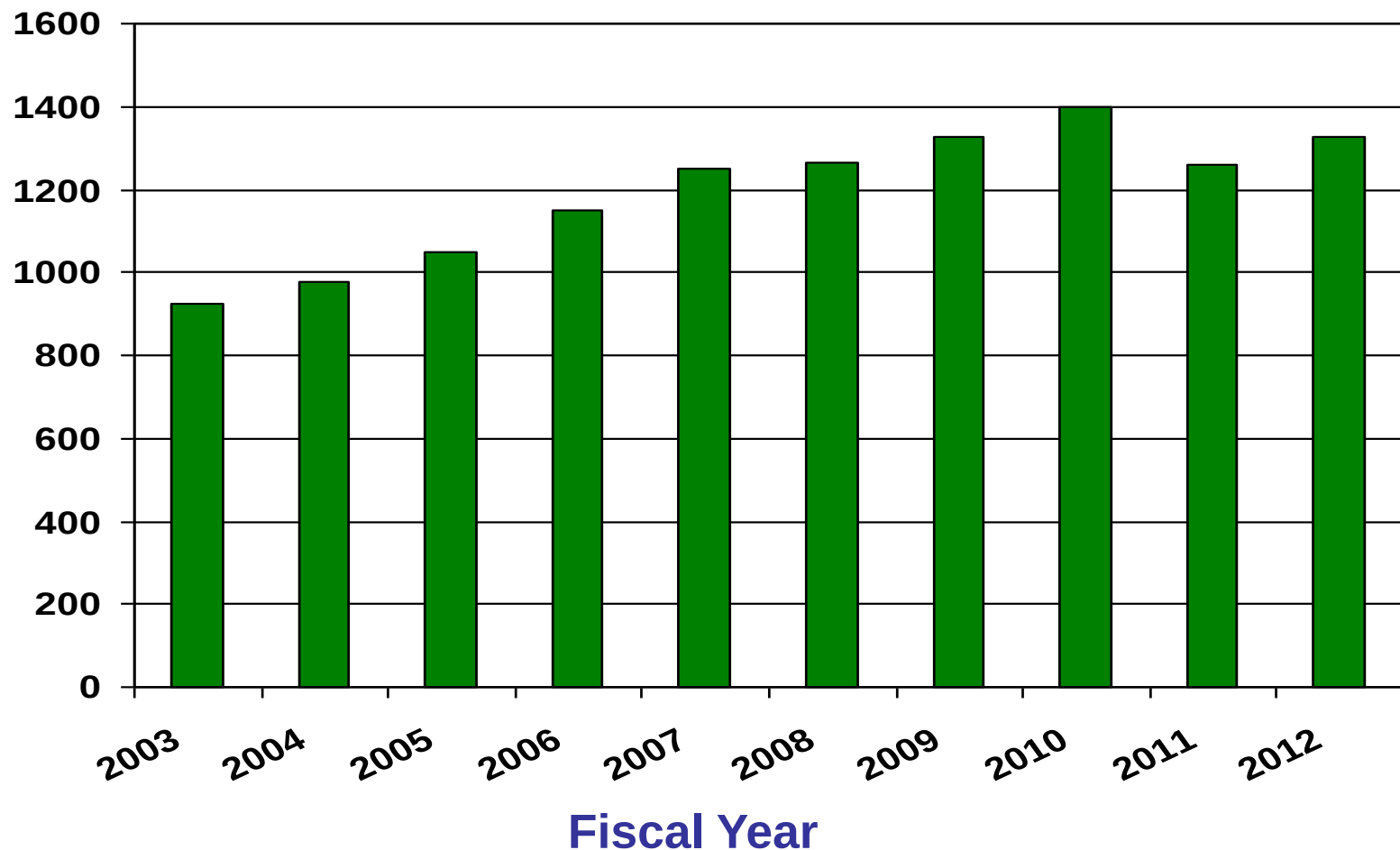
Clinical Trials

- Clinical trials require an Investigational New Drug Application (IND)
 - A formal document with defined structure and content
 - Purpose is to request exemption from premarketing requirements and to allow lawful shipment of drug for clinical investigation.
 - Regulations (21 CFR 312) outline requirements for:
 - Use of investigational drug
 - Submission of application to FDA
 - Review by FDA

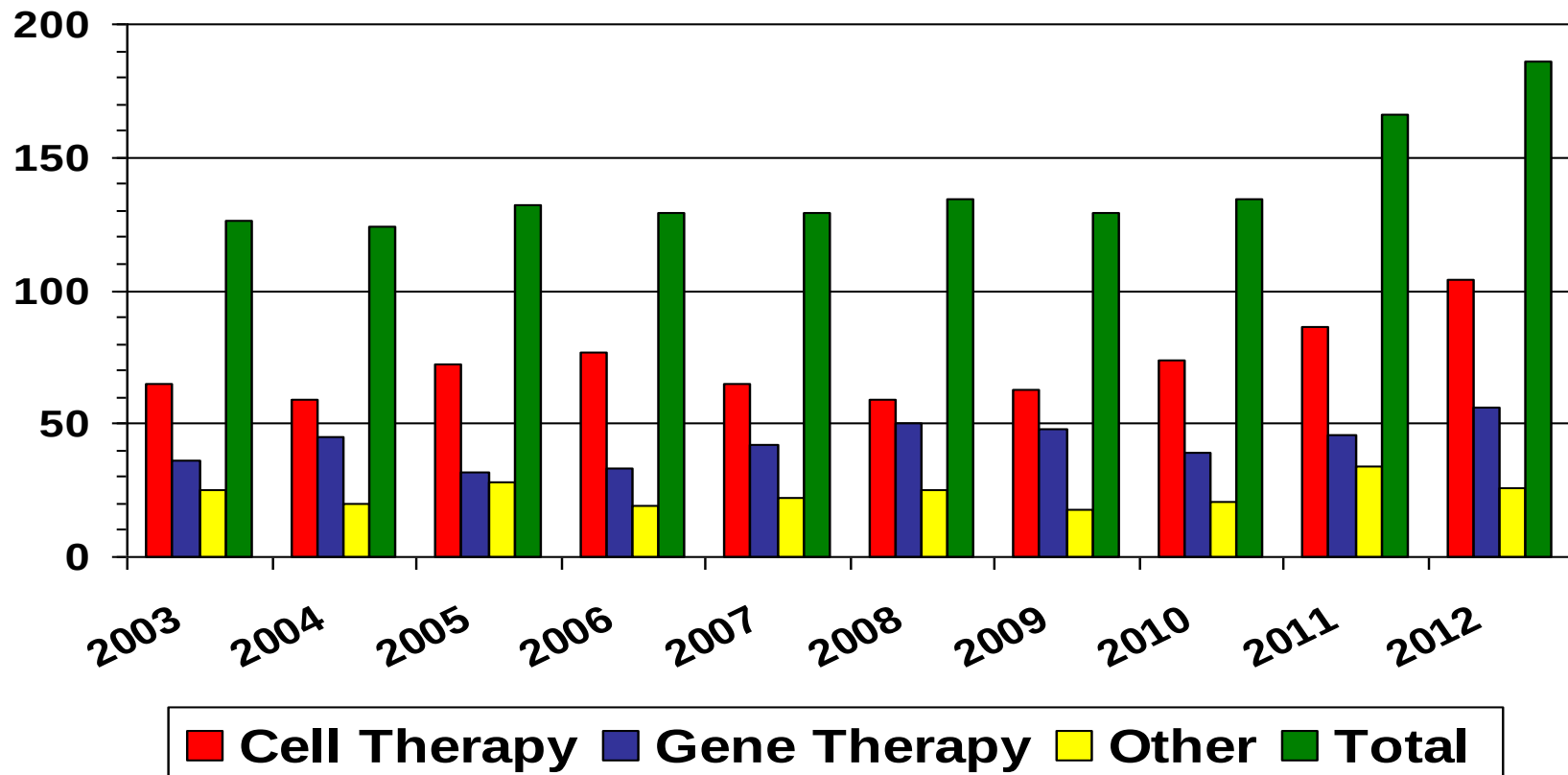
Biologics License Application (BLA)

- A request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2)
- In order to receive FDA approval the data submitted in BLA must demonstrate that the product is safe and effective for its intended use
- BLA is regulated under 21 CFR 600 – 680
- Similar to the new drug approval (NDA) process

Total Active Files in OCTGT (IND,IDE, MF) Cellular & Gene Therapies & related products



Yearly New IND and IDE Submissions to OCTGT



Cell Therapy Products with Biologic License Approvals

- Autologous cultured chondrocytes (Carticel)
Genzyme Biosurgery; 1997
- Sipuleucel-T (Provenge)
Dendreon; 2010
- Azficel-T (Laviv)
Fibrocell; 2011
- Allogeneic cultured keratinocytes and fibroblasts
in bovine collagen (Gintuit)
Organogenesis Inc; 2012

Cord Blood Products with Biologic License Approvals

- Hemacord (HPC, Cord Blood)
New York Blood Center, Inc.; Nov 2011
- HPC, Cord Blood
Clinimmune Labs; May 2012
- Ducord (HPC, Cord Blood)
Duke University School of Medicine; Oct 2012



Resources for Stakeholders

Recent CBER Guidances

- Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products (Sep 2009)
- Guidance for Industry: Cellular Therapy for Cardiac Disease (Oct 2010)
- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (Oct 2011)
- Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (Dec 2011)
- Guidance for Industry and FDA Staff: Investigational New Drug Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (Oct 2009)
- Guidance for Industry: INDs for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (June 2011)
- Guidance for Industry: Class II Special Controls Guidance Document: Cord Blood Processing System and Storage Container (March 2011)

Recent CBER Guidances (Continued)

- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) (April 2008)
- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (April 2008)
- Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (Jan 2011)
- Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular Tissue-Based Products (HCT/Ps) (December 2011)
- Draft Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2012)

OCTGT Guidance Agenda for 2013

- Draft Guidance for Industry: Early-Phase Trials of Cellular and Gene Therapies
- Draft Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
- Draft Guidance for Industry: Use of Donor Screening Tests to Test Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) for Infection with *Treponema pallidum* (Syphilis)
- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products

“OCTGT Learn” Webinars

- 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

“OCTGT Learn” Webinars: Clinical Topics posted in 2012

- Regulatory Obligations for Investigator-Sponsored Research
- Early-Phase Trials of Cellular and Gene Therapies
- Pediatric Clinical Trials
- The Target Product Profile
- Fast Track (FT) for Products Regulated in OCTGT
- IND Safety Reporting
- Data Monitoring Committees
- Endpoint Assessment and Adjudication Committees (EAACs)

OCTGT Contact Information

- Kimberly Benton, PhD
kimberly.benton@fda.hhs.gov
- Regulatory Questions:
Contact the Regulatory Management Staff in OCTGT at CBEROCTGTRMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov or by calling (301) 827-6536
- OCTGT Learn Webinar Series:
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>



Public Access to CBER

CBER website

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

Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)

Email: ocod@fda.hhs.gov

Phone: 301-827-3821

Manufacturers Assistance and Technical Training Branch (MATTB)

Email: industry.biologics@fda.gov

Phone: 301-827-4081

Follow us on Twitter

<https://www.twitter.com/fdacber>