U.S. Food and Drug Administration
Office of International Programs

Making Gene and Cell Therapy a Reality

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Acknowledgments

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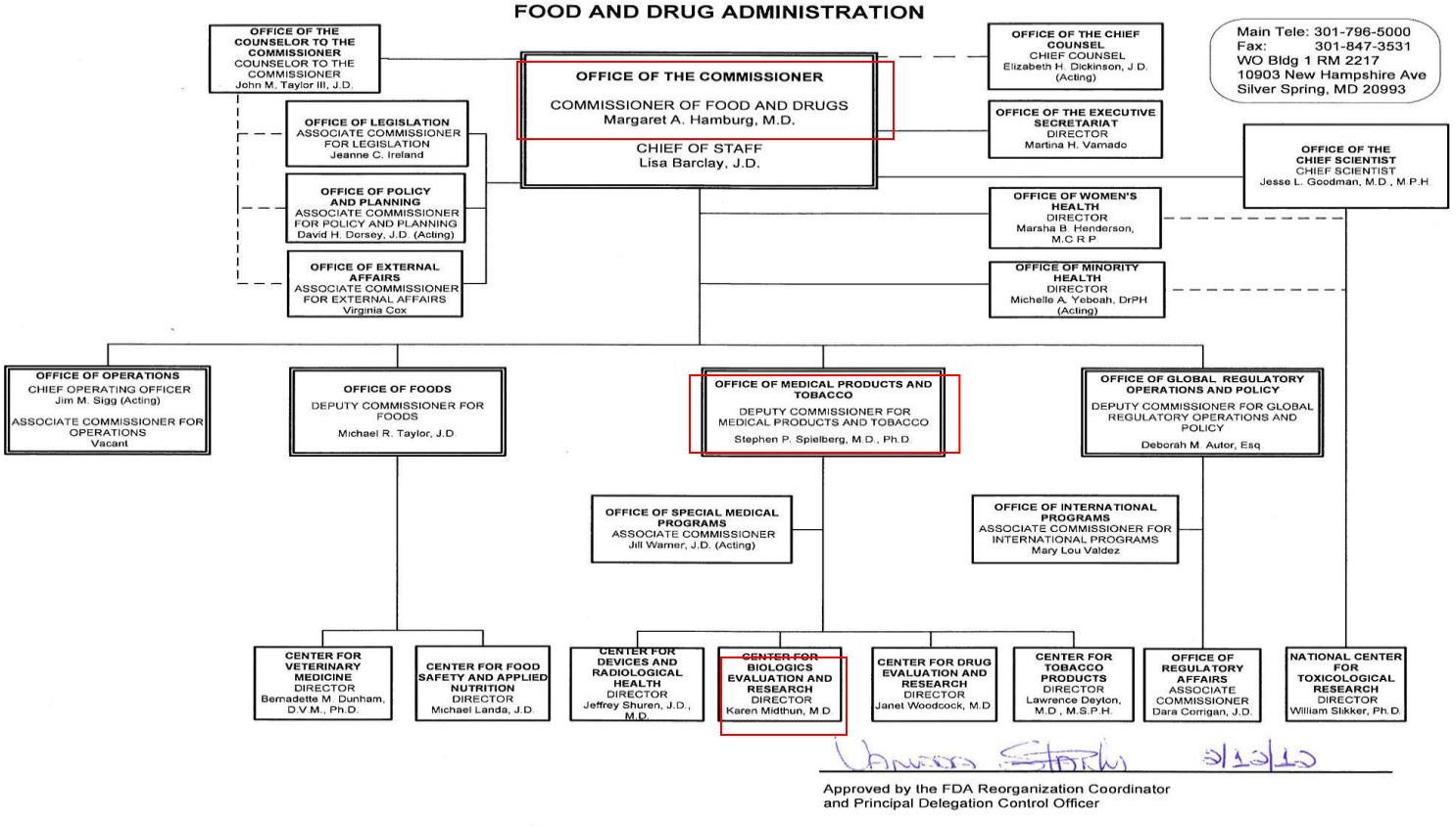
Outline

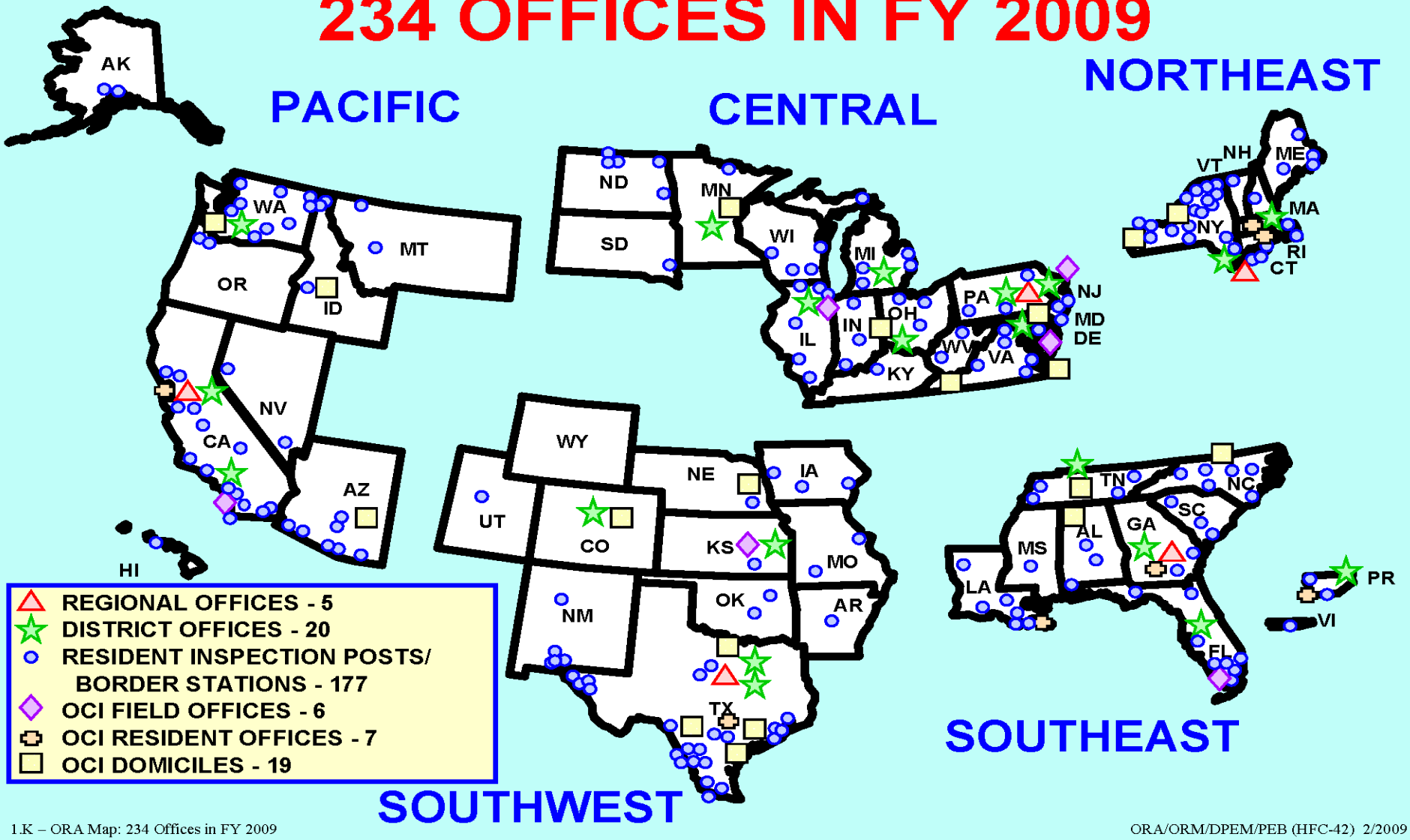
- FDA Organization and Mission
- Office of Cellular, Tissue, and Gene Therapies (OCTGT)
- Portfolio of Products
- Regulatory Framework
- Joys and Concerns
- Research, Guidances, Workshops
- International Activities

US FDA Organigramme

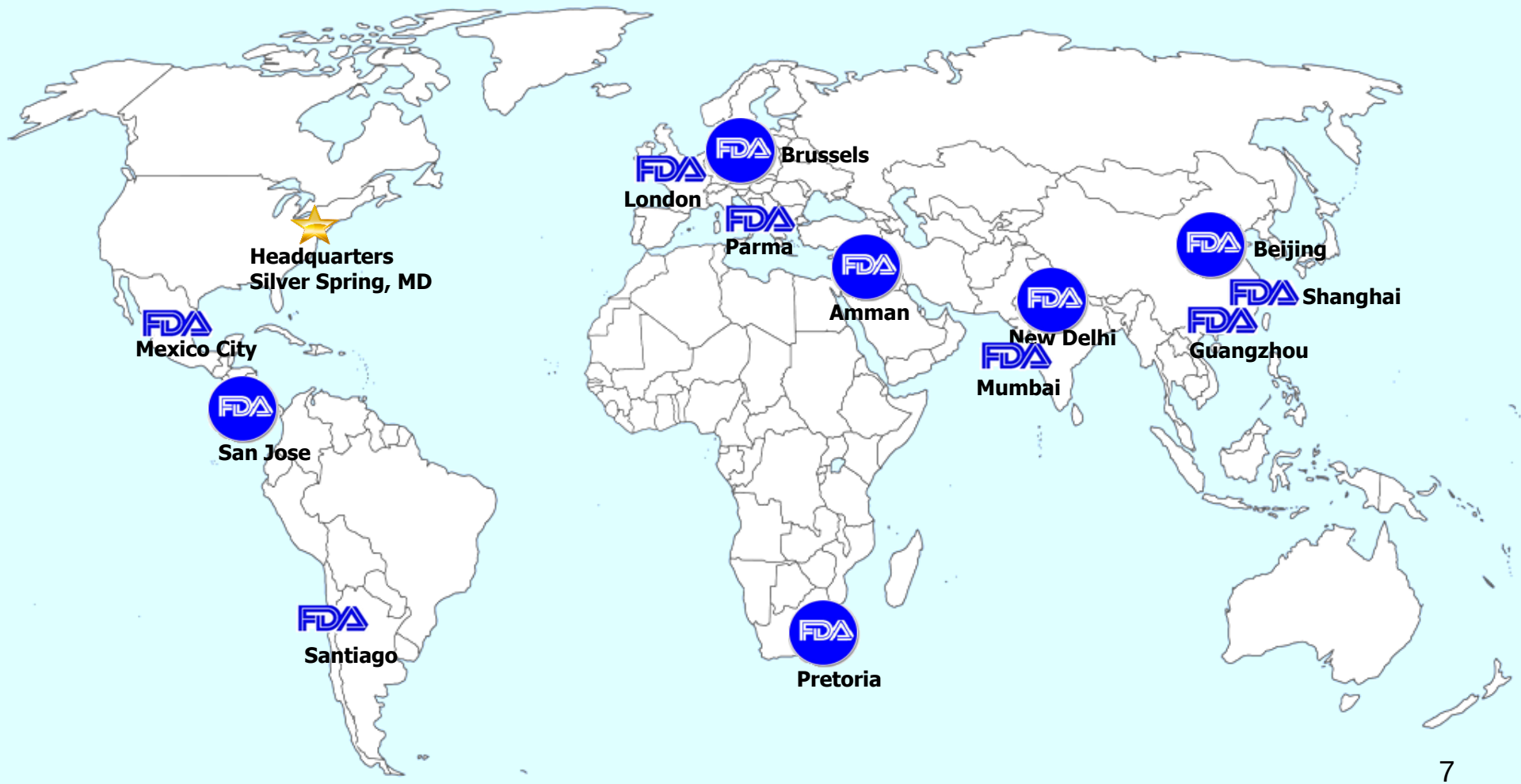


FDA's White Oak Campus

OFFICE OF REGULATORY AFFAIRS
234 OFFICES IN FY 2009



FDA Foreign Offices



Center for Biologics Evaluation and Research: Office of Cellular, Tissue and Gene Therapies

Office of Cellular, Tissue, and Gene Therapies (OCTGT)
Celia M.Witten, Ph.D, M.D., Director
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
Patrick Riggins, Ph.D., Director RPM

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

Division of Human Tissues
Ellen Lazarus, M.D., Director

Division of Clinical Evaluation and Pharmacology/Toxicology
Wilson Bryan, M.D., Director

FDA's Statutory Mission

SEC. 903. [21 U.S.C. 393] **FOOD AND DRUG ADMINISTRATION.**

(b) MISSION.—The Administration shall—

(1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;

(2) with respect to such products, protect the public health by ensuring that—

(A) foods are safe, wholesome, sanitary, and properly labeled;

(B) human and veterinary drugs are safe and effective;

(C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;

(D) cosmetics are safe and properly labeled; and

(E) public health and safety are protected from electronic product radiation;

FDA's Special International Statutory Mission

(3) … participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements…

(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

OCTGT Products

- Cellular therapies
- Gene therapies
- Tumor vaccines and immunotherapy
- Tissues/Tissue-based products
- Xenotransplantation products
- Combination products
- Devices used with cells/tissues
- Donor screening tests (for use with cadaveric blood samples)

Regulatory Framework

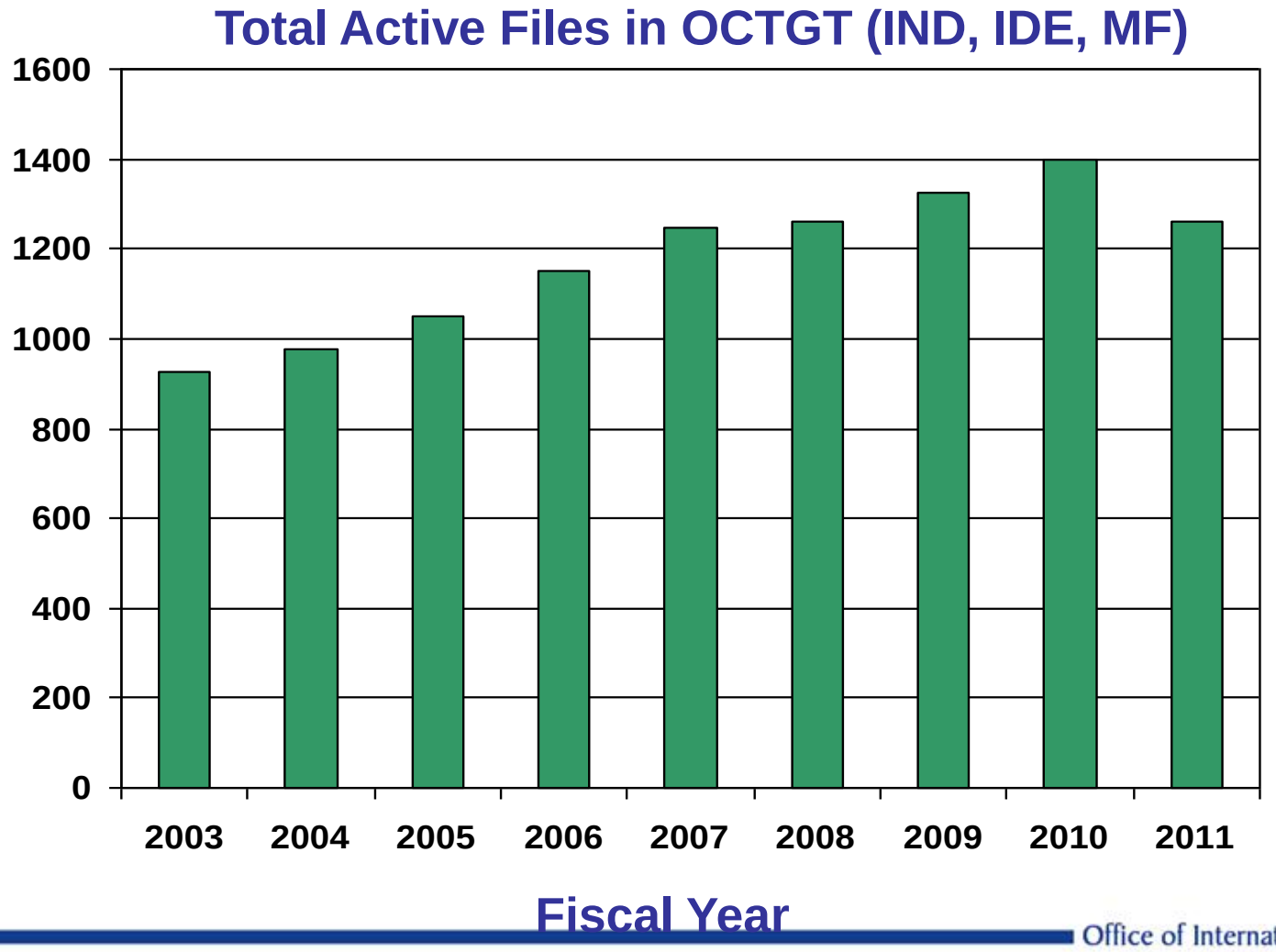
- **Federal regulatory authority is a 3-tiered system**
- **Statutes (Laws)**
  - Passed by Congress, signed into law by President
    - Food, Drug and Cosmetic Act, Public Health Service Act
- **Regulations (full force of Law)**
  - Promulgated by FDA
    - IND Regs 21 CFR 312
    - IRB and Consent Regs 21 CFR 50 and 56
    - Good Laboratory Practice 21 CFR 58
    - Human Cells, Tissues, and Cellular and Tissue-Based Products 21 CFR 1271
- **Guidance Documents (Not legally binding)**
  - Provides FDA's current thinking on specific issues

OCTGT Portfolio

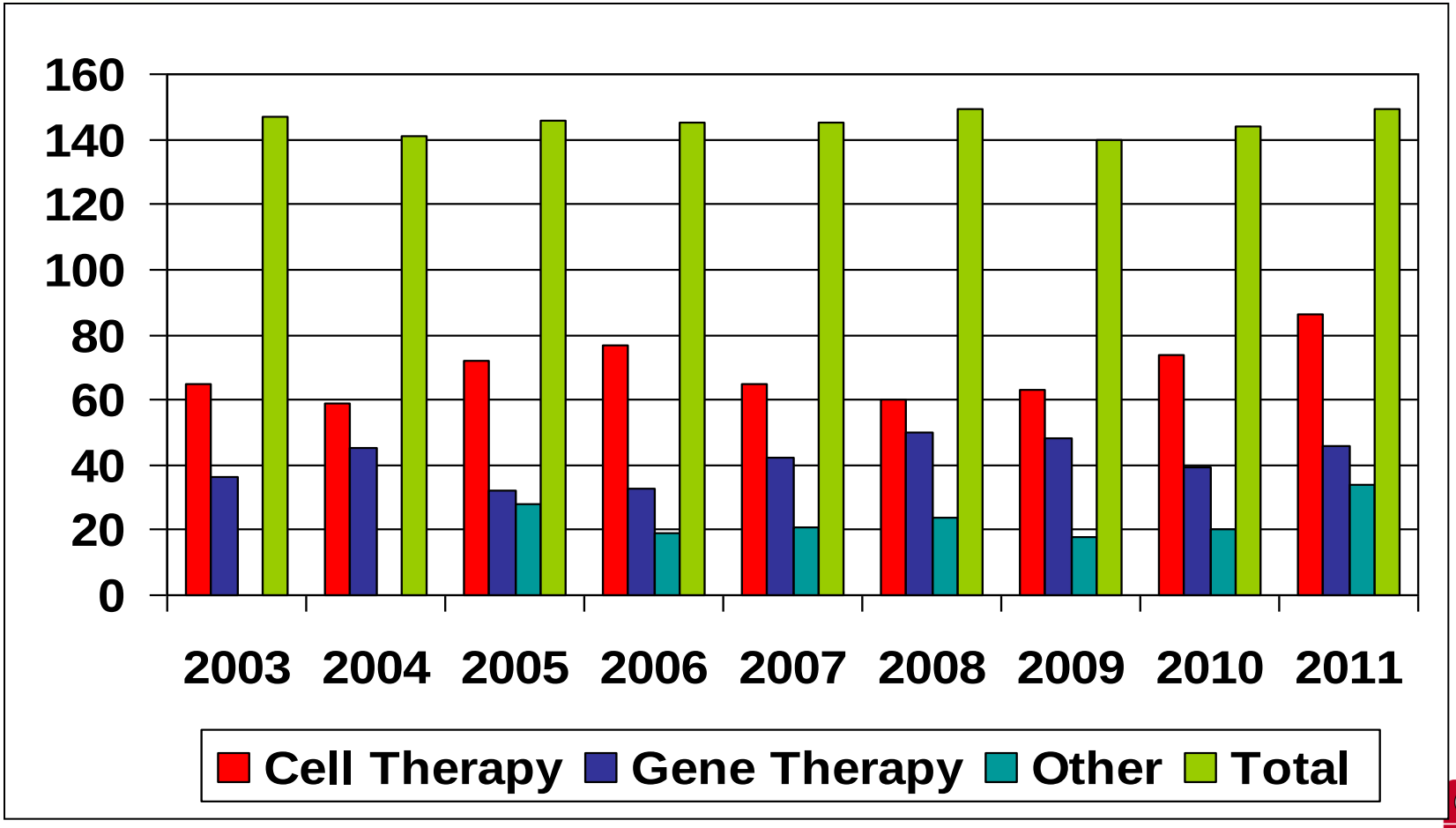
- Over 1260 active INDs and IDEs
- Four licensed products, a growing number of IND products in advanced development
- Devices: 510ks, PMAs, HDEs
- Tissue regulations
- Pre-IND advice, pre-pre-IND advice
- Policy guidance, advisory committee meetings
- Inspections and enforcement actions
- International activities

NO FEE

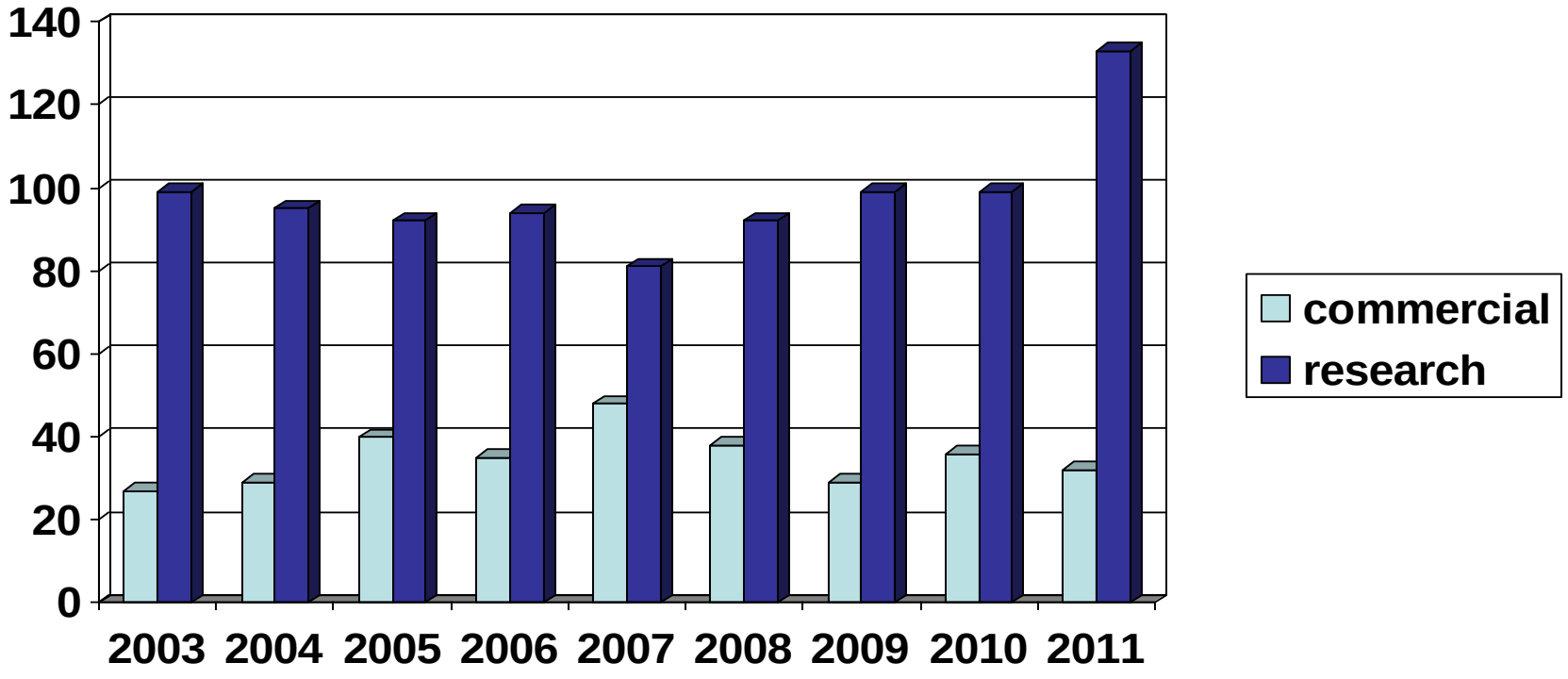
FDA Experience with Investigational Cell and Gene Therapy Products



New Submissions for Investigational Products by Year

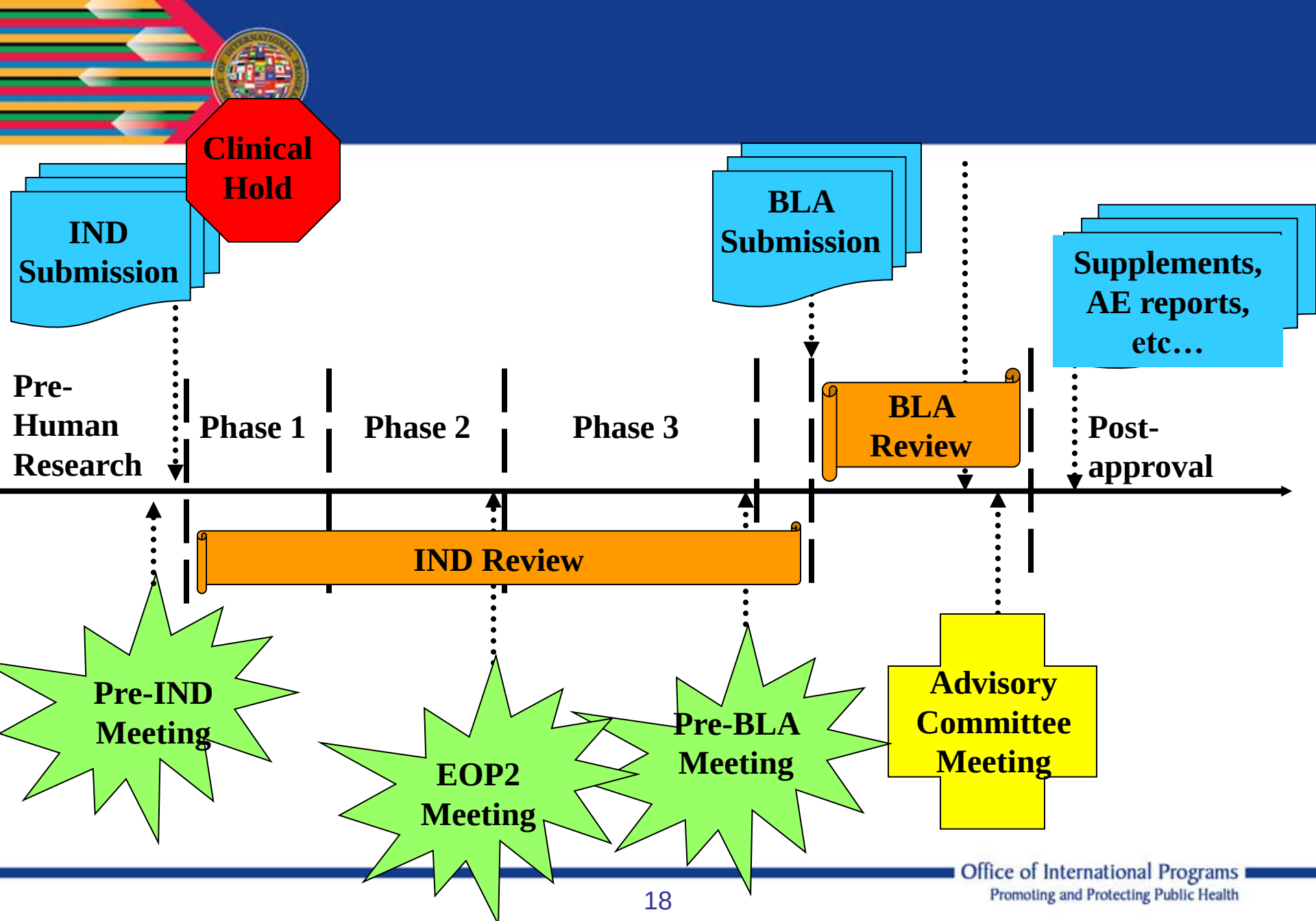


New IND and IDEs Submitted to OCTGT: Commercial or Research Sponsors



FDA Review Team

REVIEW OFFICE	CBER	FDA	OUTSIDE CONSULTANT
Review Decision	Product Quality	Scientific Expert	Patient Advocate
Project Manager	Epidemiology	Product expert	Scientific Expert (SGE)
Pharm/Tox	Statistics	Clinical specialist	Advisory Committee
Clinical	Compliance	Methodology expert	
CMC		Policy Expert	
		Orphan products	
		Ethicist	
		Animal rule	
Basic Review Team	*Extended Review Team*	*Potential Consults or Collaborators*	*Potential Consults*


Clinical Hold
IND Submission
BLA Submission
Supplements, AE reports, etc…
Pre-Human Research
Phase 1
Phase 2
Phase 3
BLA Review
Post-approval
IND Review
Pre-IND Meeting
EOP2 Meeting
Pre-BLA Meeting
Advisory Committee Meeting

Outreach: OCTGT Learn

OCTGT Learn

Office of Cellular, Tissue and Gene Therapies (OCTGT) web page for industry education.

The presenters are OCTGT staff.

Listed in next slides are the courses OCTGT currently offers.
Additional online courses are planned.

OCTGT Learn: Course List

Introduction and Scope of OCTGT

Patrick Riggins introduces the Office of Cellular, Tissue and Gene Therapies and provides a scope of what the office does.

IND Basics in OCTGT

Patrick Riggins looks at the basics of IND submission in OCTGT.

Sponsor Meetings with OCTGT

Lori Tull describes various sponsor meetings with OCTGT.

“361” Human Cells, Tissues, & Cellular and Tissue Based Products

In this presentation, Samuel Barone describes what HCT/Ps are and how they are regulated.

OCTGT Learn: Course List

The Chemistry, Manufacturing and Controls (CMC) Section of a Gene Therapy IND

Andrew Byrnes explains the basics of how to put together the CMC section of a gene therapy IND, particularly for Phase 1 trials.

Advanced Topics: Successful Development of Quality Cell and Gene Therapy Products

Denise Gavin aims to guide manufacturers toward successful development of quality cell and gene therapy products.

Cellular Therapy Products

Keith Wonnacott discusses information that is needed to prepare an investigational new drug application for a cellular therapy product.

Preclinical Considerations for Products Regulated in OCTGT

Allen Wensky provides a basic overview of preclinical considerations that make up one of the three key elements of an IND submission

The "Tissue Rules" (21 CFR 1271, Effective May 25, 2005)

- These three rules 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"), these regulations comprise the sole regulatory requirements
- For HCT/Ps regulated as drugs, devices, and/or biological products, the new tissue regulations supplement other requirements (GMP, QSR)

The "Tissue Rules" (21 CFR 1271, Effective May 25, 2005)

REGULATION	ISSUES ADDRESSED
Establishment Registration and Listing	Applicability: types and uses of products to be regulated by 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	Manufacturing to ensure that HCT/Ps do not contain communicable disease agents, are not contaminated, and do not become contaminated

21 CFR Part 1271 Applicability

- For some HCT/Ps ("361" HCT/Ps) it is the sole regulatory requirement
  - Authority from section 361 of the PHS Act
  - Prevent the introduction, transmission, or spread of communicable disease
  - No pre-market review

- Tissue Reference Group: Provides a single reference point for product-specific questions concerning jurisdiction and applicable regulation of HCT/Ps

“361” HCT/Ps

- Minimal manipulation
- Advertised/labeled for homologous use only
- Not combined with another article
- Does not have a systemic effect (except for autologous, family-related or reproductive use)

Somatic Cell Therapy Defined

- Regulated by FDA as Biologics under Public Health Service Act, section 351. FDA defined and exercised its authority in 1993.
- "Autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis or mitigation of disease or injuries"
- Do not meet the criteria in 21 CFR 1271.10 to be regulated solely under PHS Act section 361 and regulations under 21 CFR 1271

What are Human Cells, Tissues, & Cellular and Tissue Base Products (HCT/Ps)?

- **Regulatory definition: Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient**

- **Encompass a wide variety of products**

Examples of HCT/Ps

21 CFR 1271.3(d)

From deceased donors:

- Musculoskeletal tissues
- Skin
- Dura mater
- Cardiovascular tissues
- Ocular tissues
- Tissue/device and other combined products

From living donors:

- Hematopoietic stem/progenitor cells from peripheral and cord blood
- Other cell therapy products (e.g., pancreatic islets, mesenchymal stem/stromal cells, fibroblasts)
- Reproductive cells, tissues

Evolution of Stem Cell Field

Cell therapy and gene therapy products –and therefore stem cell 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 in how to fulfill the criteria

Examples of Safety Concerns: Stem Cells

- Defining the intended mode of action
- Characterization of the product, including potency
- Cell differentiation to undesired cell types
- Cell migration/trafficking to nontarget site(s)
- Potential uncontrolled cell proliferation or tumorigenicity
- Immunogenicity
- Graft-vs-host effects
- Interactions with devices, other tissues or drugs in vivo
- For gene-modified cells
  - Potential uncontrolled biological activity of the transgene
  - Alteration of expression of the nontransgenes
  - Insertional mutagenesis

Examples of CMC Issues

- Controls to prevent transmission of infection from the donor or introduction of infectious agents during cell processing
  - Donor Testing and screening for relevant communicable diseases
    - Autologous donors recommended but not required
    - Allogeneic donors must comply with 21 CFR 1271 Subpart C
      - HCT/P donor screening is medical history interview, physical assessment and medical record review
      - HCT/P donors are tested using FDA approved or cleared donor screening tests
- Cell banks- adventitious agent testing & characterization
- If mouse feeder layers used- test for the presence of murine viruses (and is a xenotransplantation product)
- Components, reagents, materials qualification

Examples of CMC Issues- 2

- Account for and control donor to donor variability
- Intrinsic safety concerns, based on cell source or history
- Adequate characterization of the product
  - Identity, purity, potency; additional characterization
- System for product tracking and labeling
  - critical for patient specific products
- Stability of product and or cell line
  - number of passages/ doublings over time
  - maintain desired differentiation properties
  - karyotypic alterations
- Product comparability for manufacturing changes

Examples of Preclinical Issues

- 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

Examples of Clinical Issues

- Collection procedure
  - Standard medical practice? Special instrument/ kit?
- Optimal dose and administration
  - Starting dose level/dose escalation scheme
  - Route of administration; dose schedule
- Define appropriate patient population
- If immunosuppression will be used:
  - Is the dose-schedule justified
  - Long-term vs short term
  - Single drug vs a combination regimen
- Safety Monitoring plans
- Safety Reporting requirements
- Pediatric issues

Outstanding Needs for the Field

- Standardized reporting/publication of results
- Technology to enable validated assays for enhanced product characterization and testing
- Biologically relevant animal species/models that will provide useful information about safety of the product
- Technology to assess biodistribution and fate of the product in patients
- Data regarding optimal timing and methods for stem cell delivery

OCTGT Research Areas

- **Stem cell-derived products** - analysis of product qualities to identify those predictive of safety and efficacy. Consortium of seven labs is characterizing preparations of MSCs, a representative product, for gene expression, genetic and epigenetic features, and many biological properties.
- **Adenoviral vectors** - biological mechanisms underlying adverse events and limited efficacy
- **Cancer therapies and vaccines** - targeting tumor-specific features for safer, more effective intervention.
- **Lentiviral vectors** - New approaches to delivering gene therapy to intended target cells safely
- **Emerging infectious diseases** – approaches to control of influenza independent of strain or subtype
- **Tissue Safety** – development and evaluation of methods for better processing, pathogen inactivation and/or pathogen detection

Recent CBER Guidances

Pathways for developing innovative cell and gene therapy products

- Current Good Tissue Practices (CGTPs) for Manufacturers of Human Cells, Tissue and Cellular and Tissue-Based Products (HCT/Ps)(Dec 2011)
- Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (Dec 2011)
- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (Oct 2011)
- 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: Potency Tests for Cellular and Gene Therapy Products (Jan 2011)
- Guidance for Industry: Cellular Therapy for Cardiac Disease (Oct 2010)

Workshops and Webinars on Cellular Products

- Pluripotent Stem Cells in Translation: Early Decisions (March 2011)
- Public Workshop on Cell and Gene Therapy Clinical Trials in Pediatric Populations (Nov 2010)
- Cord Blood Licensure: A Workshop (March 2010)
- OCTGT Learn Webinar Series
- As Part of Preparedness: FDA Public Meeting on Animal Models
- Essential elements to address efficacy under the Animal Rule (Nov 2010)

Advisory Committee Meetings

- Advisory Committee Meeting on testing for Replication Competent Retrovirus (RCR) Lentivirus (RCL) in Retroviral and Lentiviral Vector Based Gene Therapy Trials – November 2010
- Advisory Committee meeting on Cell and Gene Therapy Trials in Retinal Disease – June 2011
- Advisory Committee meeting on New York Blood Center BLA for umbilical cord blood - September 2011
- Advisory Committee meeting on Miltenyi Biotec HDE for CliniMACS CD34 Selection System –September 2011
- Advisory committee meeting on Organogenesis BLA for the treatment of surgically created gingival and alveolar mucosal surface defects in adults – November 2011

International Engagements

As an emerging product area, cell and gene therapies are prime area for prospective harmonization and convergence of regulatory approaches

- International Conference on Harmonisation (ICH)
- FDA-EMA ATMP “Cluster”/ Parallel Scientific Advice
- Regulatory exchanges
- Participate in the Asia Pacific Economic Cooperation Life Sciences Innovations Forum (APEC/LSIF) cell therapy priority work area; e.g., Stem Cell QA/QC Workshop, Bangkok, Thailand, July 5-7, 2011 for the purpose of regulatory convergence in area of stem cell therapies
- International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency Testing (Sept 2010)

FY 2012 Program Priorities

Guidance for Industry:

Draft – Preclinical Safety Assessment of Investigational Cellular and Gene Therapy Products

OCTGT Regulatory Resources

OCTGT Learn Webinar Series:

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

Regulatory Questions:

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Thank you

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