



Overview of Regulation of Stem Cell-Based Products by the U.S. FDA

EMA Stem Cell Workshop
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FDA 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
- } Product Offices
- 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
 - CTP
 - ORA
 - OC

Examples of OCTGT Products

- Stem cell and stem cell-derived products
 - Hematopoietic, mesenchymal, embryonic, etc
- Somatic cell therapies
 - Pancreatic islets, chondrocytes, myoblasts, keratinocytes, hepatocytes,
- Cancer vaccines and immunotherapies
 - Dendritic cells, lymphocyte-based therapies, cancer cell-based therapies, peptides, proteins
- Cell lysates and extracts
- Gene therapies
 - Gene modified cells
 - Plasmids, viral vectors, bacterial vectors
- Devices
 - Cell-based devices
 - Devices used for cells and tissues

Regulatory Framework

Federal regulatory authority is a 3-tiered system

- Statutes (Laws)
 - passed by Congress and signed by the President
 - Food, Drug & Cosmetic Act, Public Health Service Act
- Regulations
 - details of the law
 - written by the Agency and approved by the Executive Branch
 - 21 CFR
- Guidance Documents
 - the Agency's interpretation of the Regulations
 - written and approved within the Agency
 - advice, not binding on Agency or Industry

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 IND is in effect

(exempting the study from the premarketing approval requirements that are otherwise applicable)

Definitions

- **Drug** (21 USC 201(g)) - Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and...to affect the structure or any function of the body of man or other animals
- **Biologic** (42 USC 351(i)) - Virus, Therapeutic Serum, Toxin or Antitoxin, Vaccine, Blood, Blood Component or Derivative, Allergenic Product , Protein (except any chemically synthesized polypeptide), or Analogous Product, ... applicable to the prevention, treatment, or cure of a disease or condition of human beings
- **Device** (21 USC 201(h)) - An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article which is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; or... to affect the structure or any function of the body of man or other animals; And does not achieve its primary intended purposes through chemical action within or on the body of man and is not dependent on being metabolized to achieve its primary intended purposes

Definitions- 2

- **Combination Product** (21 CFR 3.2 (e)(1)) - A product composed of two or more components which would normally be regulated under different regulatory authorities (e.g., biologic + device, biologic + drug) that are physically, chemically, or otherwise combined or mixed and produced as a single entity
- **Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/Ps)** 21 CFR 1271.3 d): Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient

HCT/PS

Examples:

- Musculoskeletal tissue
- Skin
- Ocular tissue
- Human heart valves
- Dura mater
- Reproductive tissue
- Hematopoietic stem/progenitor cells
- Other cellular therapies
- Tissue/device & other combination therapies

Excluded:

- Vascularized human organs
- Minimally manipulated bone marrow
- Xenografts
- Blood products
- Secreted or extracted products; e.g., human milk, collagen, cell factors
- Ancillary products used in manufacture
- In vitro diagnostic products
- Blood vessels recovered with organs for use in organ transplantation

Regulatory Categories for HCT/Ps

- **Exempt:** exclusions on previous slide, autologous product reimplanted during the same surgical procedure, minimally manipulated marrow for homologous use, or reproductive cells implanted into the partner of the donor.
- **“361 Product”:** PHS 361 and 21 CFR 1271 apply; no premarket review required if ALL of the following criteria are met:
 - 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
- **“351 Product”** – Not exempt and not solely a 361 product.
 - Premarket review required.
 - Regulatory path of Biologic or Device according to which definition is applicable.

Stem Cell-Based 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)
 - Cell therapy
 - Gene therapy- when genetic material is transferred to cells ex vivo

Guidances



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 for 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

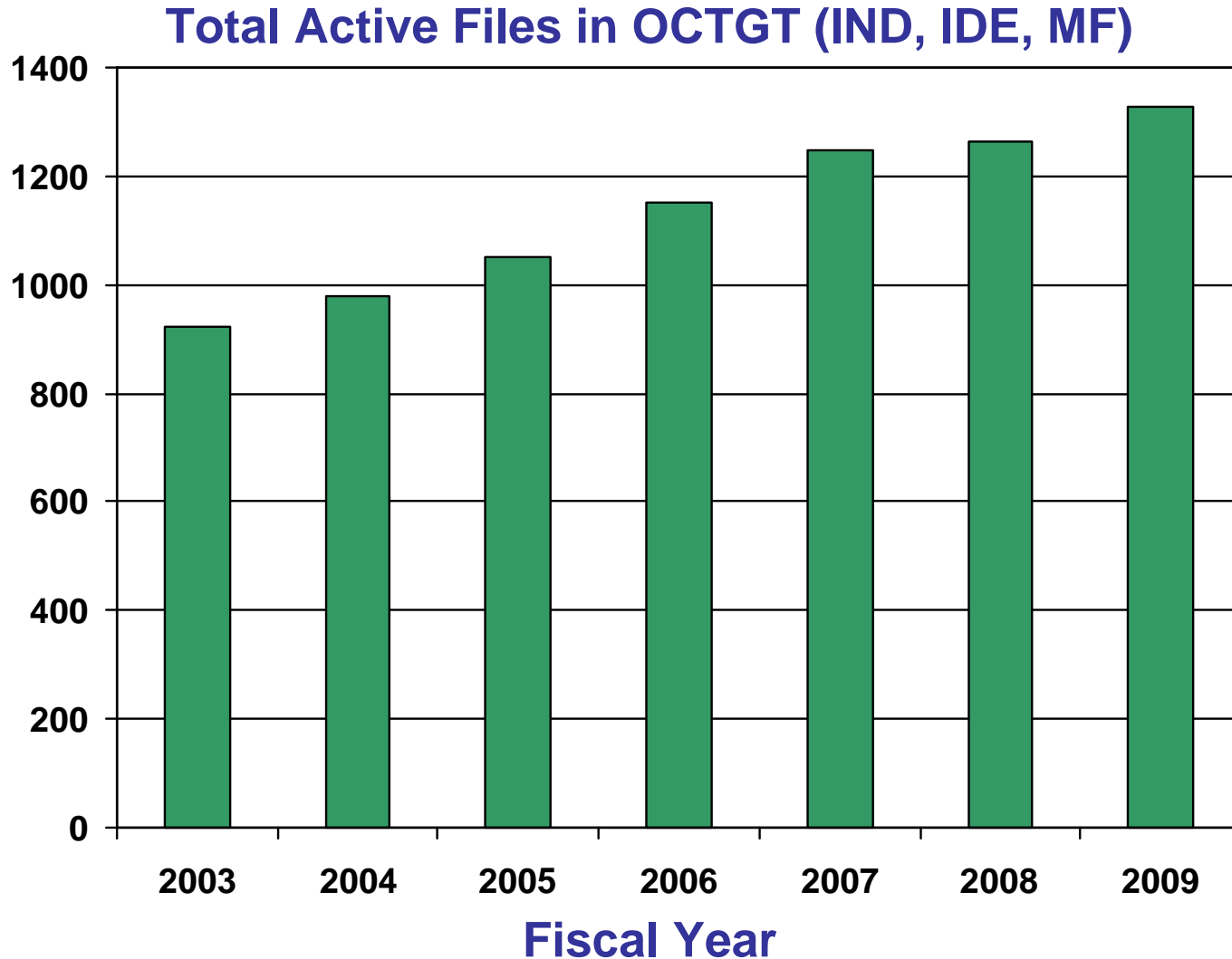
Examples of Clinical Issues

- Collection procedure
 - Standard medical practice? Special instrument or 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

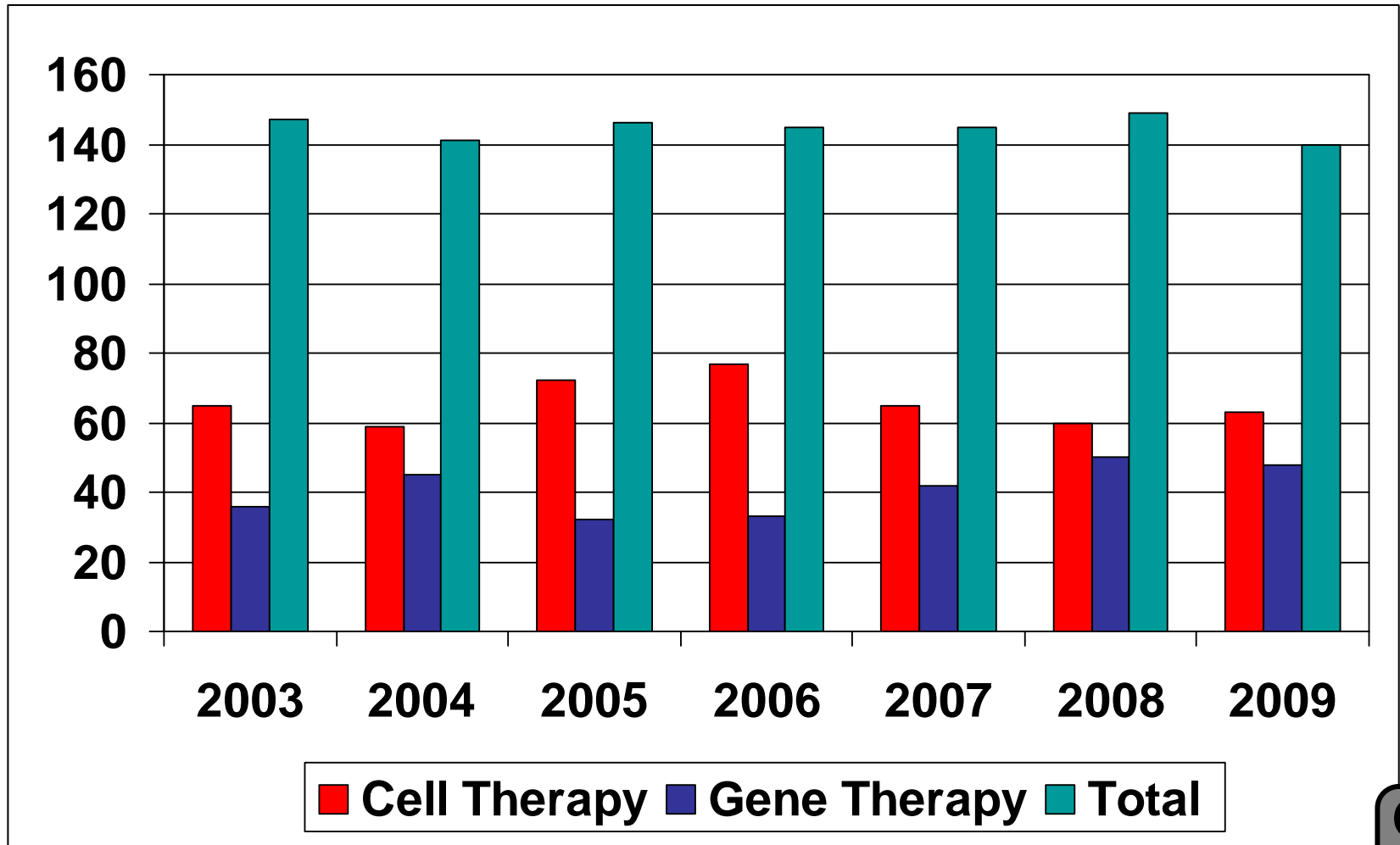
Administration of Stem Cell Products

- Delivery of stem cells to certain anatomic locations may require novel procedures and/or novel delivery devices
 - This needs to be considered early
- Cells delivered by certain devices (i.e. catheter) will be a Combination Product
 - Cells under Biologics/Drug regulations and Device under Device regulations (see 21 CFR 3.2(e))
 - Early consultation with FDA, and Device manufacturer, about regulatory aspects
- Compatibility of cells with the device
- Preclinical testing of cells and device
- Delivery procedure used during clinical trial and beyond
 - Training of clinical investigators

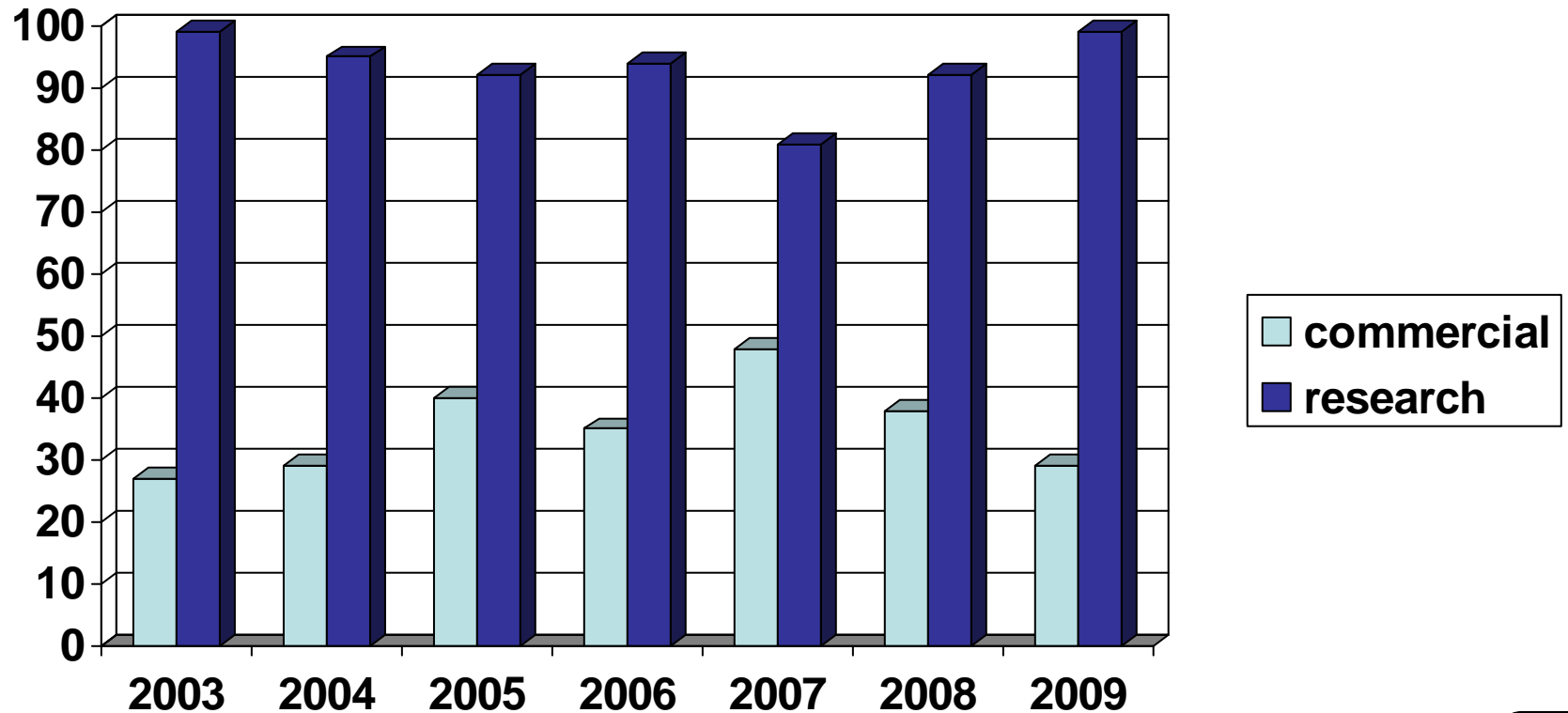
FDA Experience with Investigational Cell and Gene Therapy Products



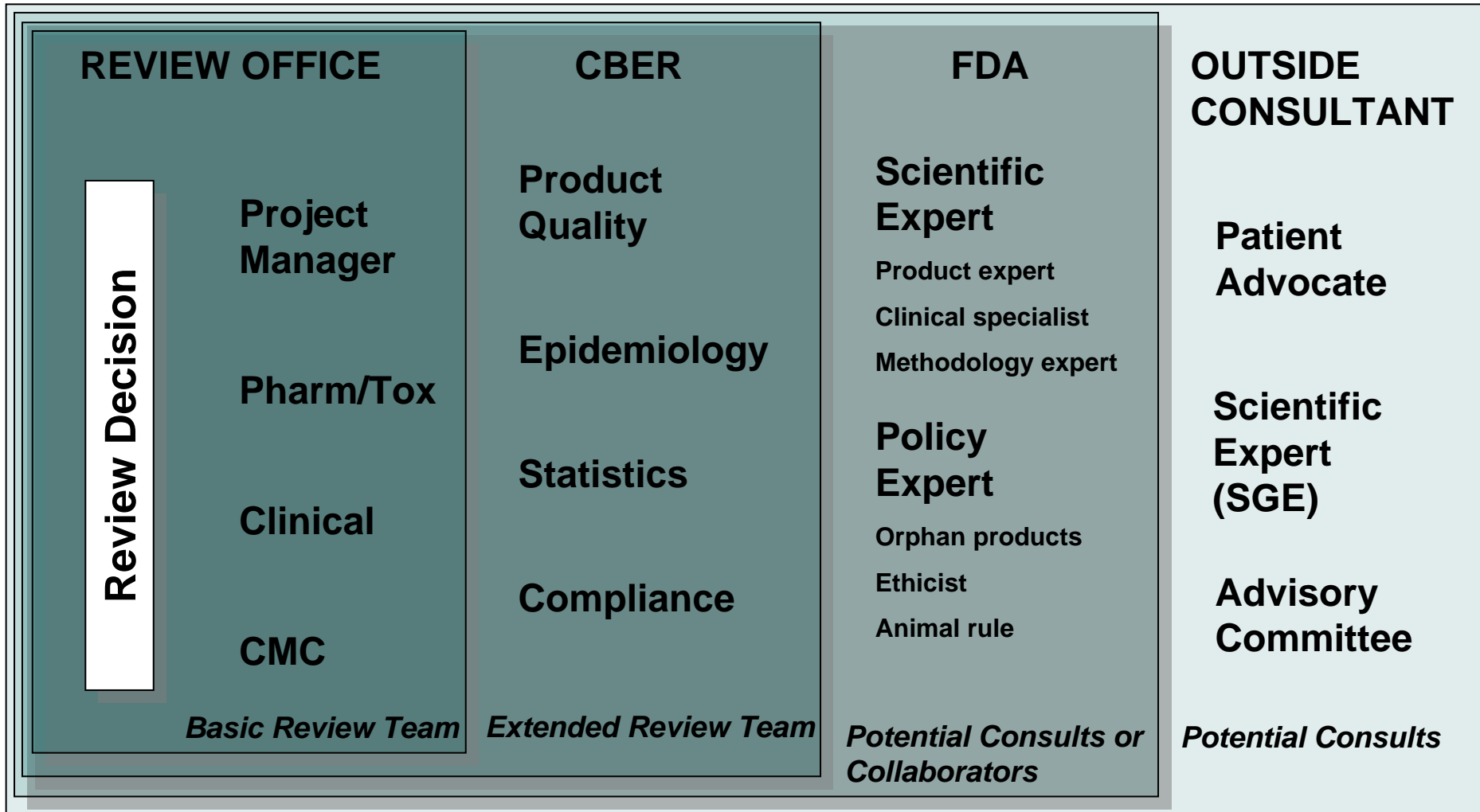
Yearly New Submissions for Investigational Products



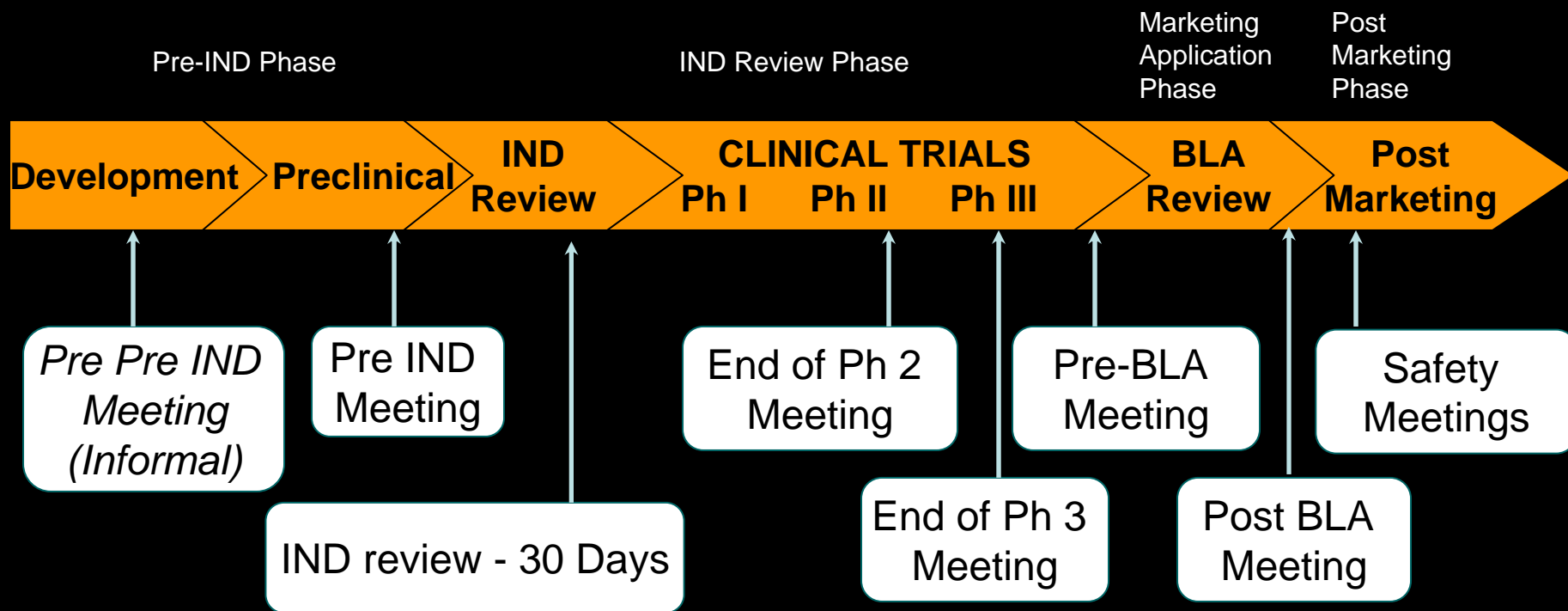
New Applications - Commercial or Research Sponsors



FDA Review Team



Scientific Advice from the FDA



- Provide advice in response to specific queries
- In person or by teleconference
- Written minutes for formal meetings
- No fee

CBER Outreach to Stakeholders

- Advisory Committees
- Regulations
- Guidance Documents
- Workshops
- Liaison Meetings
- International Harmonization

Public Discussions of the Issues

- Nov 9 2009 NIH/JDRF/FDA Workshop: Next Generation Beta-Cell Transplantation
- Oct 27 2009 FDA/NCI Workshop: Therapeutic Cancer Vaccines Considerations for Early Phase Clinical Trials Based on Lessons Learned from Phase III
- May 14 2009 CTGTAC: Animal Models for Porcine Xenotransplantation Products Intended to Treat Type 1 Diabetes or Acute Liver Failure
- May 15 2009 CTGTAC: Products Intended to Repair or Replace Knee Cartilage
- Mar 13 2009 FDA/NIH/CIBMTR/ASBMT Workshop: Clinical Trials Endpoints for Acute Graft-Versus-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation
- April 10 2008 CTGTAC: Safety of Cell Therapies Derived from Human Embryonic Stem Cells
- Topics prior to 2008:
 - Cellular Replacement Therapies for Neurological Disorders
 - Placental/Umbilical Cord Blood For Hematopoietic Reconstitution
 - Allogeneic Pancreatic Islets for Type 1 Diabetes
 - Cellular Products for the Treatment of Cardiac Disease
 - Cellular Products for Joint Surface Repair
 - In Vitro Analyses of Cell/Scaffold Products
 - Insertional Mutagenesis by Retroviral Vectors

Contact Information

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- **OCTGT Regulatory Issues**
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- **General information for OCTGT and related regulatory references**
 - <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm>