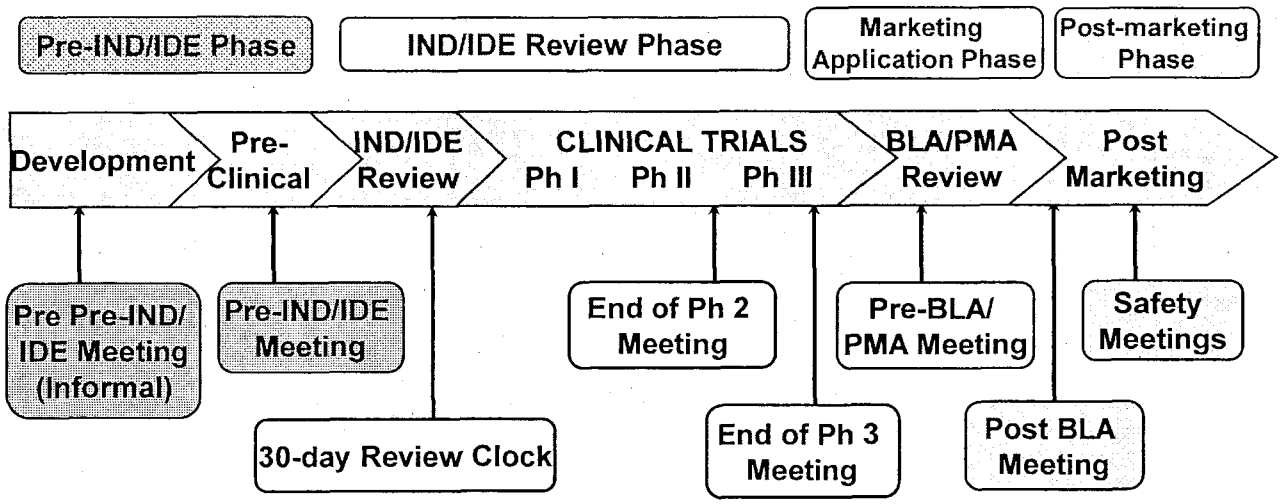
Reviewer Expertise

- Training
  - Education/Experience
  - On-the job
    - Scientific and regulatory meetings
    - Mentoring
    - Internal working group
    - Career development
      - clinical service, laboratory and clinical research
    - Research/Review model
      - Laboratory based review staff
        - » ~ 50% review, 50% research

Phases of Investigational Studies (21 CFR 312.21)

- Phase I Investigational Studies
  - Designed to evaluate safety and side effects
- Phase 2 Investigational Studies
  - Expanded safety; evaluates efficacy
- Phase 3 Investigational Studies
  - Emphasis efficacy, additional information on safety; expanded study

Interactions with FDA Throughout the Product Lifecycle



Product development is an iterative process, with frequent FDA and sponsor interaction

Combination Product

- 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
- Guidance:
  - Early Development Considerations for Innovative Combination Products (2006): http://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm

Determining Classification and Lead Review Center for Combination Products

- Publically Available Resources
  - Meetings and workshops
  - Classification and Jurisdictional Information (FDA website): http://www.fda.gov/CombinationProducts/JurisdictionalInformation/default.htm
- Center Jurisdictional Officer
  - Informal jurisdictional inquiries
- Office of Combination Products (OCP)
  - OCP Jurisdictional Updates
  - Informal assignment requests
  - Request for Designation (RFD): classification and jurisdiction assignments made based on primary mode of action (PMOA) determination, inter-center agreements, most relevant expertise, and/or precedence

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Cell-Device Combination Products Regulated by OCTGT

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

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
  - Equipment
- Product Safety and Quality testing
- Product Stability
- Other controls- product container labels, tracking
- Product comparability (when applicable)

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Product Characterization: Specifications-why you need them

- Demonstrate Product Consistency
- Control purity and impurity profiles of the final product.
  - Identify characteristics that predict safety and clinical effectiveness
  - Detect cells with undesired characteristics
- Demonstrate control of the Manufacturing Process.
  - Quality Assurance/Quality Control Program
- Ensure product integrity and stability.
- Identify product parameters that anticipate adverse events.

Biologic Product Specifications: Codified in Regulation *(CFR Specifications)*

Product should be characterized with reference to its:

- Safety (610.11, 610.12, 610.30, 610.40)
  - Sterility (bacterial and fungal sterility)
  - Endotoxin
  - Mycoplasma
  - Tests for opportunistic viruses
- Purity (610.13)
  - Free of extraneous materials
- Identity (610.14)
  - Specific test to distinguish it from others
- Constituent Materials (610.15)
  - Ingredients, Preservatives, Diluents, Adjuvants, Excipients
- Potency (610.10)
  - Assay for biological function

Potency

- Measured bio-activity: ability or capacity to achieve intended effect
  - Direct measure of biological activity
    - In vivo or in vitro assay
  - Indirect measure of biological activity
    - Analytical assay methods: non-bioassay method directly correlated to a unique and specific activity of the product
  - Multiple Assay Approach (Assay Matrix)
    - May not be possible or feasible to develop a single assay that encompasses all elements of an acceptable potency assay
- BLA: validated functional bioassay
- Relate data to appropriate Reference Standard
- A US regulatory requirement for biologics

Purpose of Potency Testing

- Demonstrate that each product "lot" manufactured has biological activity within established limits
- Demonstrate product consistency
  - Lot to lot, Patient to patient
- Demonstrate product stability
- Aid interpretation of clinical data

Challenges for testing cell therapy products

- Small lot size/limited sample volume
- Limited shelf life (due to cell viability)
- Limited availability of starting material for process, product, and test method development
- Lack of reference standards
- Patient to patient variability and cellular heterogeneity
- Multiple potential mechanisms of action