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Development of Regenerative Medicine Products: FDA Perspectives

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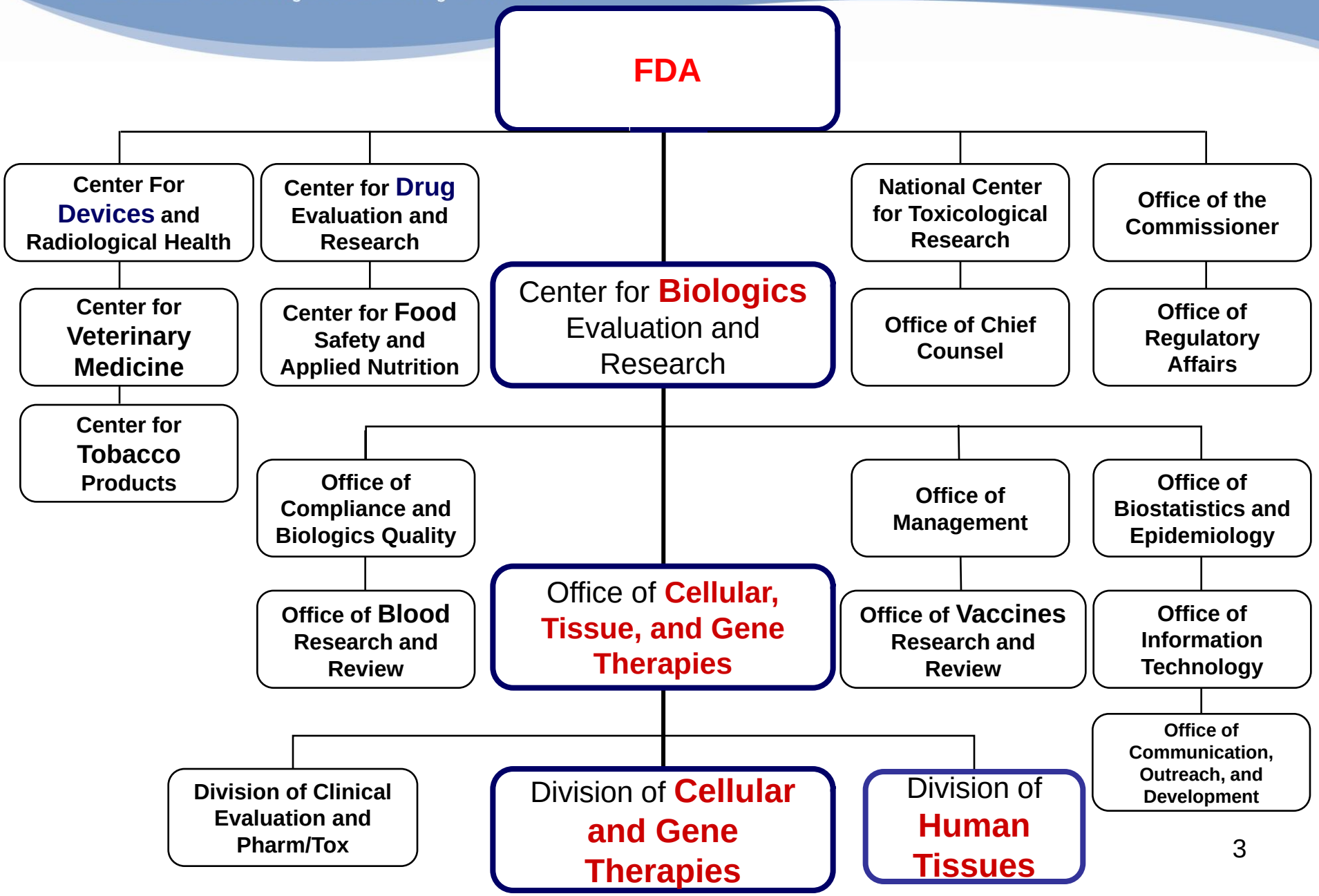
Regulatory Framework: 3-Tiered System

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

  Written and approved within FDA
  - Advice non-binding on FDA or sponsor


FDA
Center For Devices and Radiological Health
Center for Drug Evaluation and Research
National Center for Toxicological Research
Office of the Commissioner
Center for Veterinary Medicine
Center for Food Safety and Applied Nutrition
Center for Biologics Evaluation and Research
Office of Chief Counsel
Office of Regulatory Affairs
Center for Tobacco Products
Office of Compliance and Biologics Quality
Office of Management
Office of Biostatistics and Epidemiology
Office of Blood Research and Review
Office of Cellular, Tissue, and Gene Therapies
Office of Vaccines Research and Review
Office of Information Technology
Office of Communication, Outreach, and Development
Division of Clinical Evaluation and Pharm/Tox
Division of Cellular and Gene Therapies
Division of Human Tissues

What is and 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 (e.g., cells or tissue + device)

Not regulated as HCT/P's

- Vascularized human organs
- Minimally manipulated unrelated donor bone marrow
- Xenografts-separate regulatory pathway
- Blood and blood products - separate regulatory pathway
- Blood vessels recovered with organs and used for organ transplantation only
- Autologous cells recovered and used in same surgical procedure

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 CRF 1271)
  - The Establishment Registration, Donor Eligibility and Good Tissue Practice (GTP) final rules comprise 21 CFR Part 1271
- **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)
  - Regulatory path: **Biologic** (IND/BLA) or **Device** (IDE/PMA)

Cellular Therapies

- Regulated as HCT/P and subject to 1271 regulations
- Regulated as drugs and biologics and subject to premarket review requirements
- 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

Regulation of Cell Therapies Under the 1271 Tissue Rules

HCT/P's regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 ONLY IF ALL FOUR of the following are met:

- Minimally Manipulated: Relevant biologic characteristic(s) are not altered by processing.
- Homologous Use Only: The HCT/P performs the same basic function in the recipient as in the donor.
- Production of the HCT/P does not involve combination of cells with another **article** (with limited exceptions and on the condition that addition of the excepted article does not raise new clinical safety concerns).
- Does not have a systemic effect, is not dependent upon the metabolic activity of living cells for primary function: exceptions for (a) autologous use, (b) first- or second-degree blood relatives, or (c) reproductive use.

More than Minimal Manipulation

- Risk of adventitious virus introduction during manufacturing
  - Reagents
  - Operators
  - Environment
- Risk of alteration of biological properties
  - Manufacturing is a novel, non physiological microenvironment

Risk/Benefit Considerations

- Protect patients from unreasonable risk
- Case-by-case
  - Patient population
    - Age
    - Medical condition
    - Availability of other treatment
    - Previous experience with similar products
  - Clinical Trial Design
  - Preclinical Information
  - Product Characteristics and Characterization

Team Approach to Regulation of Regenerative Medicine Products

- Review Team
  - Product
  - Clinical
  - Pharm/Tox
  - Statistician
  - Regulatory Project Manager
  - Consult reviewer(s)
- CBER Research/Reviewer Model
  - Scientists/Clinicians: research-reviewers and full time review staff

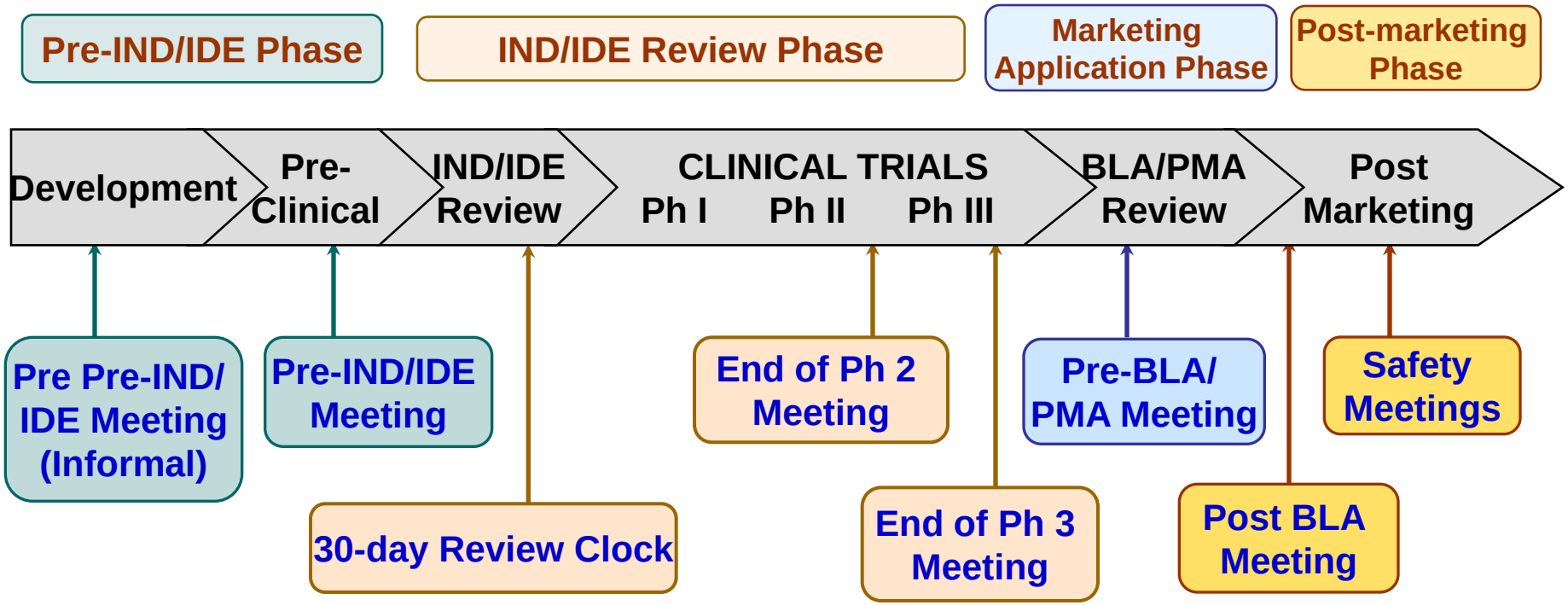
Reviewer Expertise

- 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

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)

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

Advice on Preparing For Pivotal Studies-Product

- Understand critical product characteristics & have the controls in place to maintain consistency
- Have meaningful potency assay in place
- Lock down procedures and acceptance criteria based on development experience
- Protocol for stability of Phase 3 material in place, based on earlier stability data
- Shipping qualification

Lot Release Specifications- are you there?

- Guidance: ICH Q6B, Q6A
- Step-wise approach:
  - Phase 1: safety, quality manufacture
  - Phase 2: safety, tightening specifications
  - Phase 3: safety, specifications defined
  - BLA:
    - Validated assays
    - Statistical analyses
- Inability to understand critical product characteristics can impact ability to analyze clinical data

Pre-Clinical

- 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: 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

Planning Later Phase Clinical Studies

- End of phase 2 meeting with FDA
  - Justify dose, regimen for phase 3
  - Preliminary safety profile established
  - Target population
    - Specific proposed indication
    - Assays required for eligibility
    - Prior therapy
  - Proposed control arm
  - Statistical considerations
  - Assessments
  - Preliminary evidence of activity/effect size
- Estimate patient effect size for phase 3 planning
  - Interpretation of time to events is problematic in single arm studies
    - Leads to over optimistic interpretation of effect size

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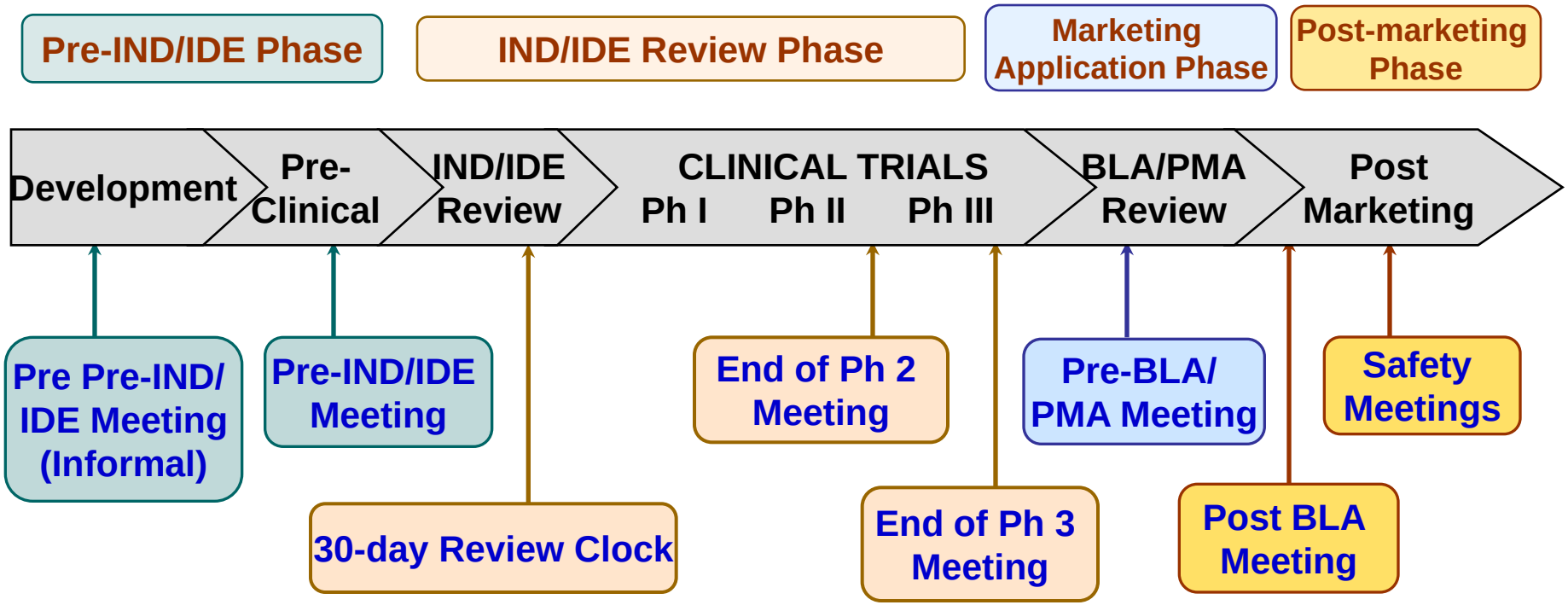

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Legal Standard for New Drug Approval

- Adequate tests of safety under the conditions prescribed, recommended or suggested in labeling
- Substantial evidence of effectiveness under the conditions prescribed, recommended or suggested in labeling
- Manufacturing, processing and packing is adequate to assure identity, strength [potency], quality and purity

-- Section 505(d)

Examples of mechanisms for ensuring product safety and efficacy

- License application review
- Clinical data auditing and site inspections
- Pre-approval and biennial manufacturing facility inspections
- Appropriate product labeling
- Post marketing commitments and requirements
- Monitoring of adverse event and product deviation reporting

OCTGT Resources & Contact Information

- **References for the Regulatory Process for OCTGT:**
  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
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