



U.S. Food and Drug Administration

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# FDA's Clinical Investigator Course

## *Preparing an IND Application: CBER*

### *Breakout Session*

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Center for Biologics Evaluation and Research  
Food and Drug Administration**

*Cosponsored by*

*FDA's Office of Critical Path Programs (OCPP)  
and  
The Clinical Trials Transformation Initiative (CTTI)*

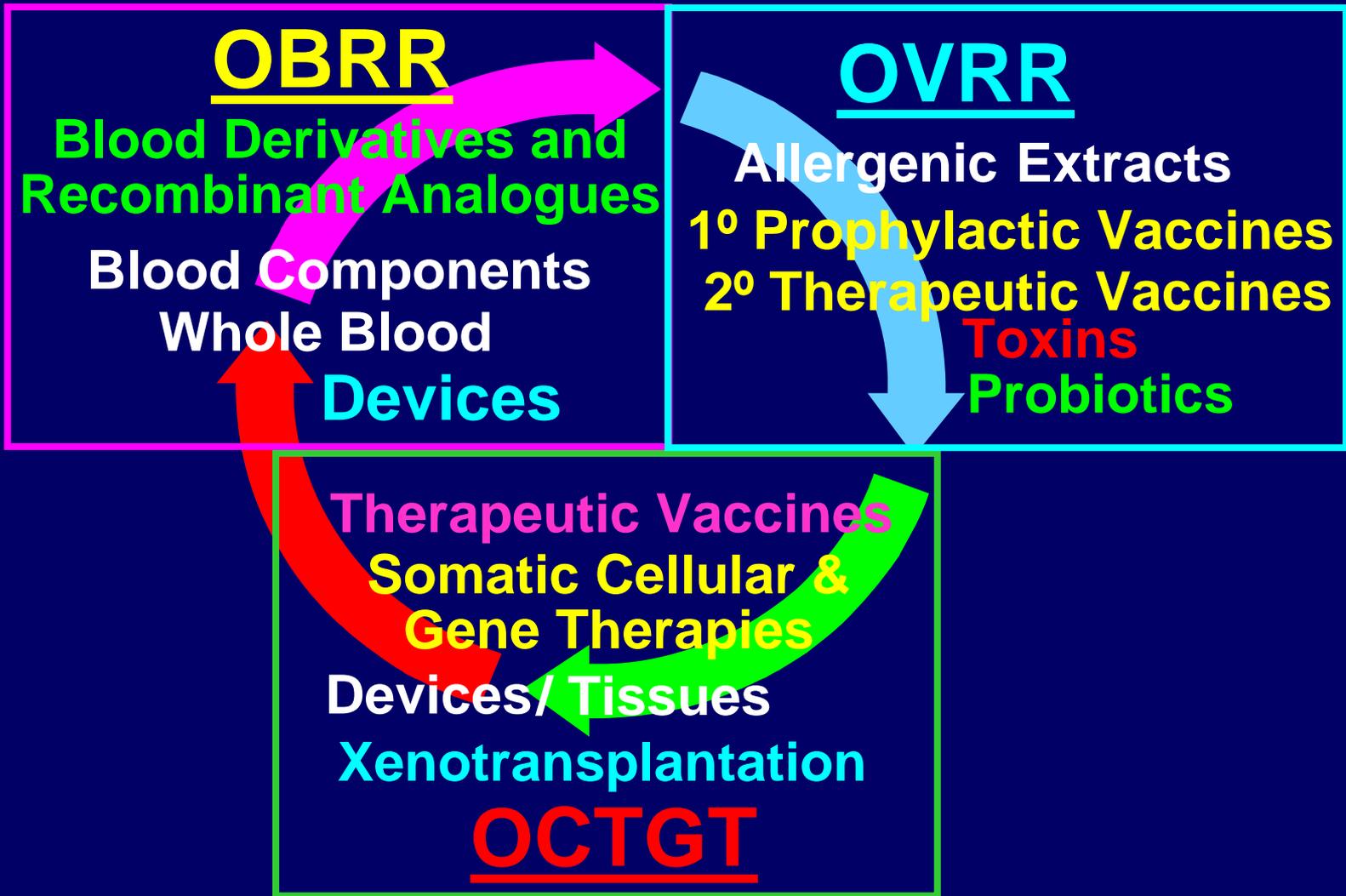


U.S. Department of Health and Human Services

Food and Drug Administration



# Products Regulated by CBER



# ■■■ Cellular Therapies: Applying Tissue Regulations – 21 CFR §1271

**21 CFR 1271.3(d)**- Articles consisting of / derived from human cells or tissues intended for implantation, transplantation, infusion, or transfer, into a human recipient regulated as human cells, tissues and cellular and tissue-based products (HCT/Ps)

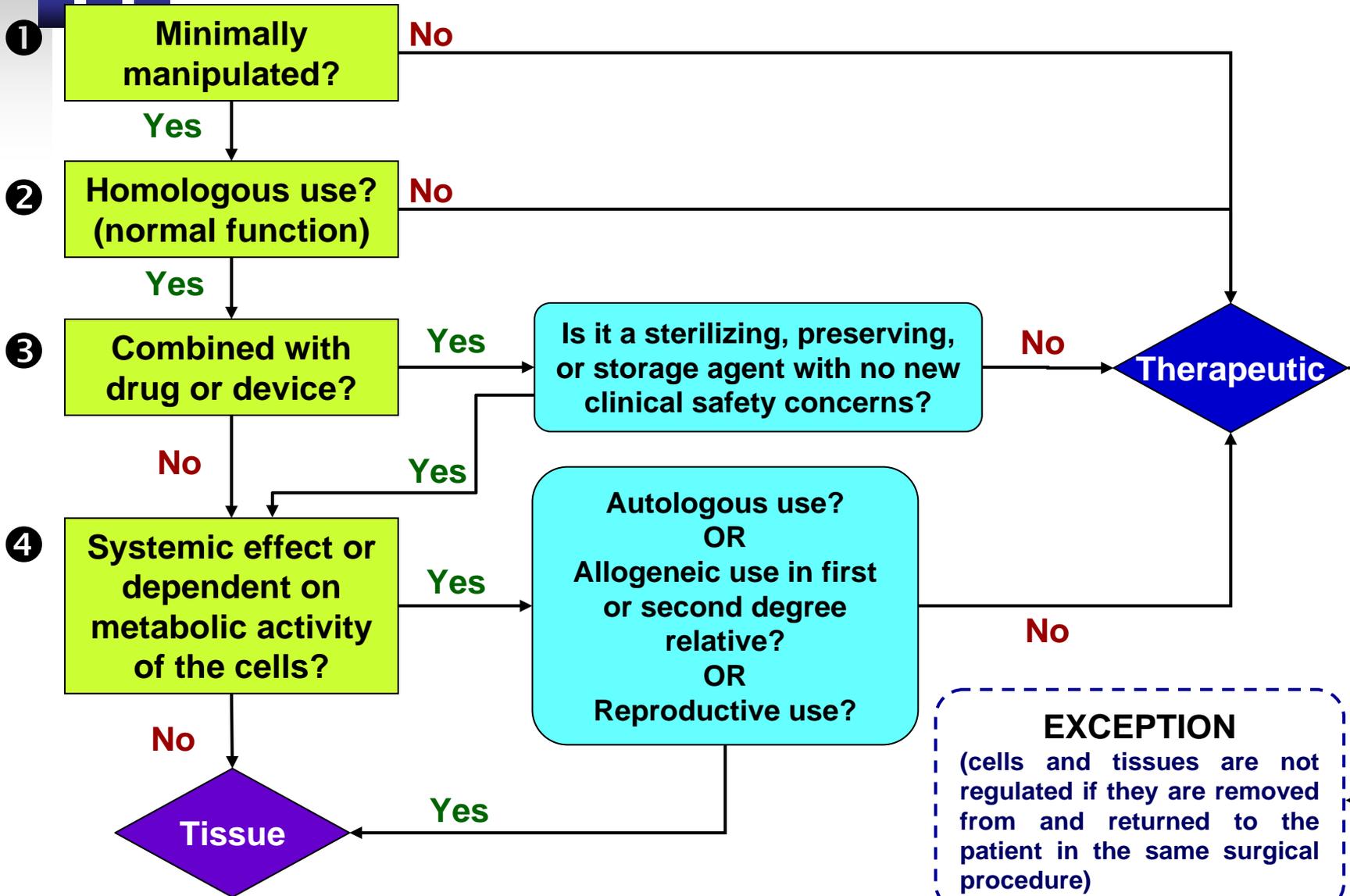
**HCT/Ps may be eligible for regulation as tissues solely under Section 361 of the PHS Act and 21 CFR § 1271**



# HCT/P Regulation Solely Under Section 361 and 21 CFR 1271

**ONLY when 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 or functions in the recipient as in the donor.
- ▶ **Production of the HCT/P does not involve combination of cells with another article**: (limited exceptions and on the condition that addition of the excepted article does not raise new clinical safety concerns).
- ▶ **No systemic effect, 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.

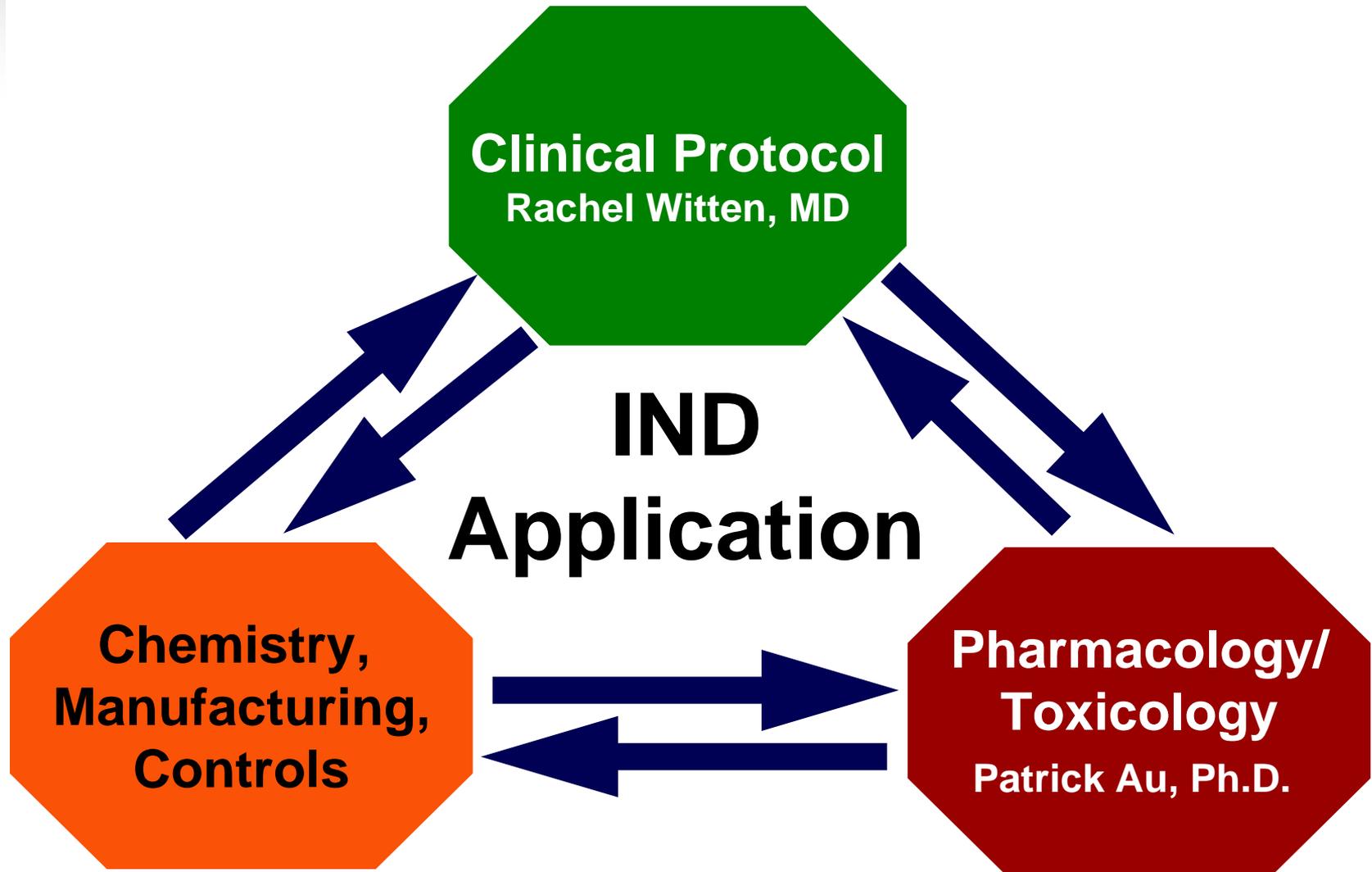


**EXCEPTION**  
 (cells and tissues are not regulated if they are removed from and returned to the patient in the same surgical procedure)

# 361 Tissue of IND Required?

- ▶ **Mononuclear cells collected by apheresis from partially-matched, related family donor following growth factor treatment to mobilize stem cells from the marrow compartment into the circulation**
- ▶ **Apheresis product is enriched for hematopoietic stem cells and depleted of allo-reactive T-lymphocytes using an FDA-approved, cell selection device**
- ▶ **Enriched stem cell population is washed with physiologic solution, suspended in a cryoprotectant and cryopreserved until use**
- ▶ **Day of treatment, stem cell-enriched, T-cell-depleted product is thawed and infused into patient following completion of myeloablative chemotherapy regimen for a hematologic malignancy to support hematopoietic reconstitution and promote GVL response**

# Key Elements of the IND Submission



# ■ ■ ■ 21 CFR 312.20 Subpart B: IND Application

<input type="checkbox"/>	Form FDA 1571	21 CFR 312.23(a)(1)
<input type="checkbox"/>	Table of Contents	21 CFR 312.23(a)(2)
<input type="checkbox"/>	Introductory statement and general investigational plan	21 CFR 312.23(a)(3)
<input type="checkbox"/>	Investigator's brochure	21 CFR 312.23(a)(5)
<input type="checkbox"/>	Protocols	21 CFR 312.23(a)(6)
<input checked="" type="checkbox"/>	<b>Chemistry, manufacturing, and control data</b>	<b>21 CFR 312.23(a)(7)</b>
<input type="checkbox"/>	Pharmacology and toxicology data	21 CFR 312.23(a)(8)
<input type="checkbox"/>	Previous human experience	21 CFR 312.23(a)(9)
<input type="checkbox"/>	Additional information	21 CFR 312.23(a)(10)

# Information Provided in CMC Section Should Demonstrate.....

## Ability to consistently and reproducibly manufacture your investigational cellular product using:

- ➔ Well-controlled manufacturing process that relies on practices and procedures executed according to standardized written procedures.
- ➔ Qualification program for source materials, reagents, ingredients, excipients and components used throughout the manufacturing process.
- ➔ In-process and final product release testing that demonstrates overall product quality and safety/sterility.



# Helpful Reference: Preparing CMC Section for Cellular Product IND

## Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications

<http://www.fda.gov/downloads/BiologicsBloodVaccines/Guidance/ComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm092705.pdf>



# CMC Guidance: Information to Include in IND Submission

## I. PRODUCT MANUFACTURING/CHARACTERIZATION

### • Components and Materials

- ➔ **Cells**: Autologous or Allogeneic, cell source/type (stem/progenitor or functionally specialized), description of characteristic attributes
- ➔ **Reagents/Materials/Excipients**: List of all used during manufacturing process, indicate whether clinical grade. Describe qualification program for acceptance

### • Manufacturing Procedures

- ➔ Provide an outline of the manufacturing process for the cellular product including timing for specific steps and overall duration
- ➔ Describe facility where manufacturing takes place, list equipment used, provide information about the qualifications of persons responsible for performing manufacturing
- ➔ Indicate final formulation, unit dosage, total number of units produced per manufacturing run, and method of storage if product not given fresh



## II. PRODUCT RELEASE TESTING/RESULTS

- **Microbiological Testing**

- ➔ **Sterility Testing (Bacterial/Fungal)**: Performed according to test specified in 21 CFR 610.12 or indicate if using alternative test method (over time need to demonstrate equivalence of test methods)
- ➔ **Mycoplasma**: Performed when manufacturing process involves extended periods of cell culture. May use recommended culture based assay, or PCR / other alternative test method (demonstrate adequate sensitivity/specificity). Test sample composition important
- ➔ **Adventitious Agents**
  - ✓ For cells recovered from allogeneic, unrelated donors: perform donor eligibility determination for communicable diseases
  - ✓ Cell Banks (Master and Working): In vivo and in vitro test methods for viral adventitious agents as appropriate



## II. PRODUCT RELEASE TESTING/RESULTS (2)

- **Identity:** assay that is specific for the cellular product, able to uniquely identify product from others that may be manufactured in the same facility
- **Purity:** testing performed to demonstrate the final product is free from undesired extraneous materials introduced during the manufacturing process.
  - ➔ Residual Contaminants: Assays to detect the presence of residual substances including cytokines, growth factors, antibodies, magnetic beads and serum used during manufacturing process and purification.
  - ➔ Pyrogenicity/Endotoxin (manufacturing process impurities)



## II. PRODUCT RELEASE TESTING/RESULTS (3)

- **Potency:** Tests for potency shall consist of either *in vitro* or *in vivo* tests, or both, which have been specifically designed for each product so as to indicate its potency
  - ➔ **Potency** is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests....to effect a given result.
  - ➔ **Biological Activity** is... “the specific ability or capacity of a product to achieve a defined biological effect.” A measure of potency.
  - ➔ Potency assay(s) provides quantitative measurement of a relevant biological activity identified on the basis of preclinical testing and product characterization that is indicative of a cellular product’s capacity to elicit a clinical effect.

\* General Safety Testing Not Required for Cellular Products





### III. **FINAL PRODUCT RELEASE TESTING:** **ACCEPTANCE CRITERIA** (Drug Substance = Drug Product)

- Release testing is performed on the final formulated product for each lot manufactured (could be  $N = 1$ )
- Specifications/acceptance criteria, test methods for safety (sterility), purity, identity, and potency described in IND.
- Results from final product release testing should be available prior to patient administration.
- If finalized test results will not be available prior to product/lot release, should include in IND reporting notification process in event acceptance criteria are not met.
- Perform pilot manufacturing runs that demonstrate ability to manufacture cellular product that meets release test specifications/acceptance criteria.



## IV. FINAL PRODUCT STABILITY

- IND should include description of stability testing program developed to demonstrate cellular product is sufficiently stable for use throughout the time period covered by a clinical study.
- Stability test panel should include assays to monitor product sterility, identity, purity, quality, and potency. Test results should meet specifications established prospectively.
- For each assay included in the stability test panel, you should provide a description of the test method, indicate sampling time points, and specify composition of the test article.



## V. OTHER ISSUES

- **Product Tracking/Segregation:**
  - You should include in IND submission information about adequate system to identify product from time of collection until patient administration
  - Include description of procedures developed to ensure segregation from other products manufactured in the same facility, preventing inadvertent cross-contamination
- **Labeling:**
  - Describe labeling used throughout manufacturing process and provide sample of label affixed to the final cellular product
  - Label for investigational product must contain the statement: ***“CAUTION: New Drug – Limited by Federal law to Investigational Use”***
  - Additional labeling necessary if donor eligibility testing is incomplete or not performed (e.g. cells for autologous use)



## V. OTHER ISSUES (2)

- **Processing/Manufacturing at Multiple Sites:**

When cell processing/manufacturing is performed at several participating clinical sites, you should include in your IND a description of the plan used for qualifying manufacturing performed at each site.

- **Shipping From Single Manufacturing Location to Multiple Clinical Sites.**

Your IND submission should include a summary of testing performed to qualify product shipping procedures.

- **Patient Delivery Device:**

If you will be using a novel device for product administration, or standard syringes and needles not developed for injection of a cellular product, you need to supply information in your IND demonstrating biocompatibility and uniform delivery of viable cell dose.

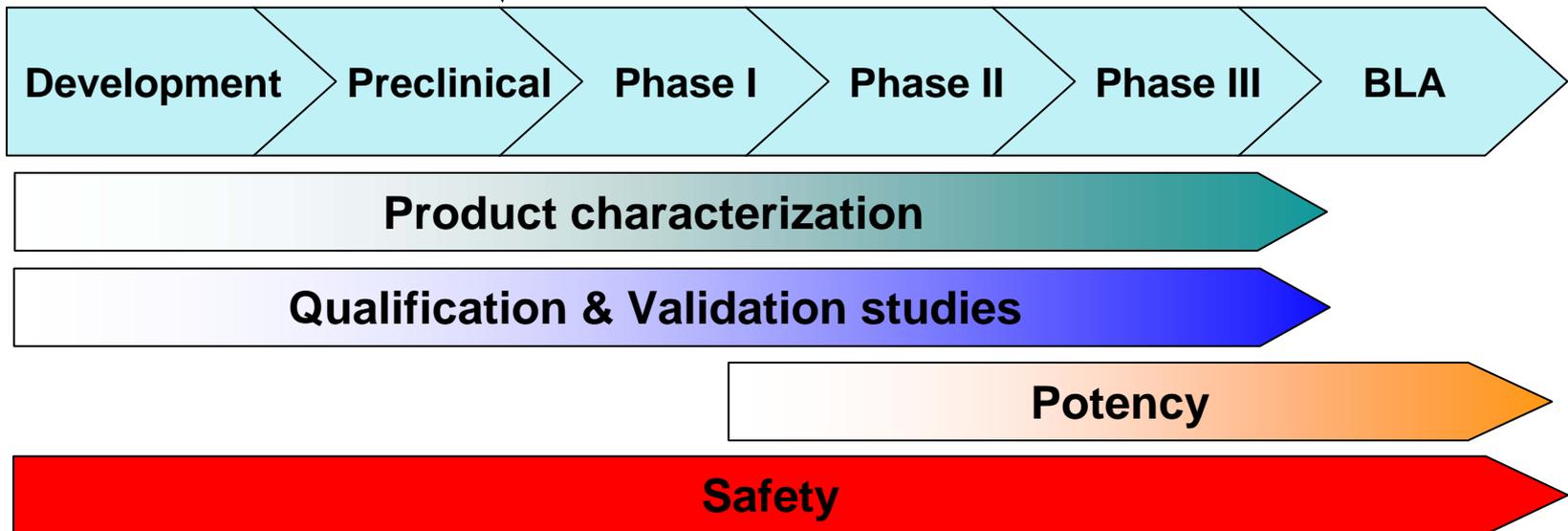


## V. OTHER ISSUES (3)

- **Lot-to-Lot Comparability**
  - ➔ Relevant when the quantity of initial source material or output of a single manufacturing run may be insufficient to generate the total number of doses necessary to complete a clinical study
  - ➔ Describe in your IND in vitro and/or in vivo preclinical testing that will be conducted to demonstrate product comparability for:
    - ✓ Separate manufactured lots produced from the same starting material OR.....
    - ✓ Separate manufactured lots produced from different starting material

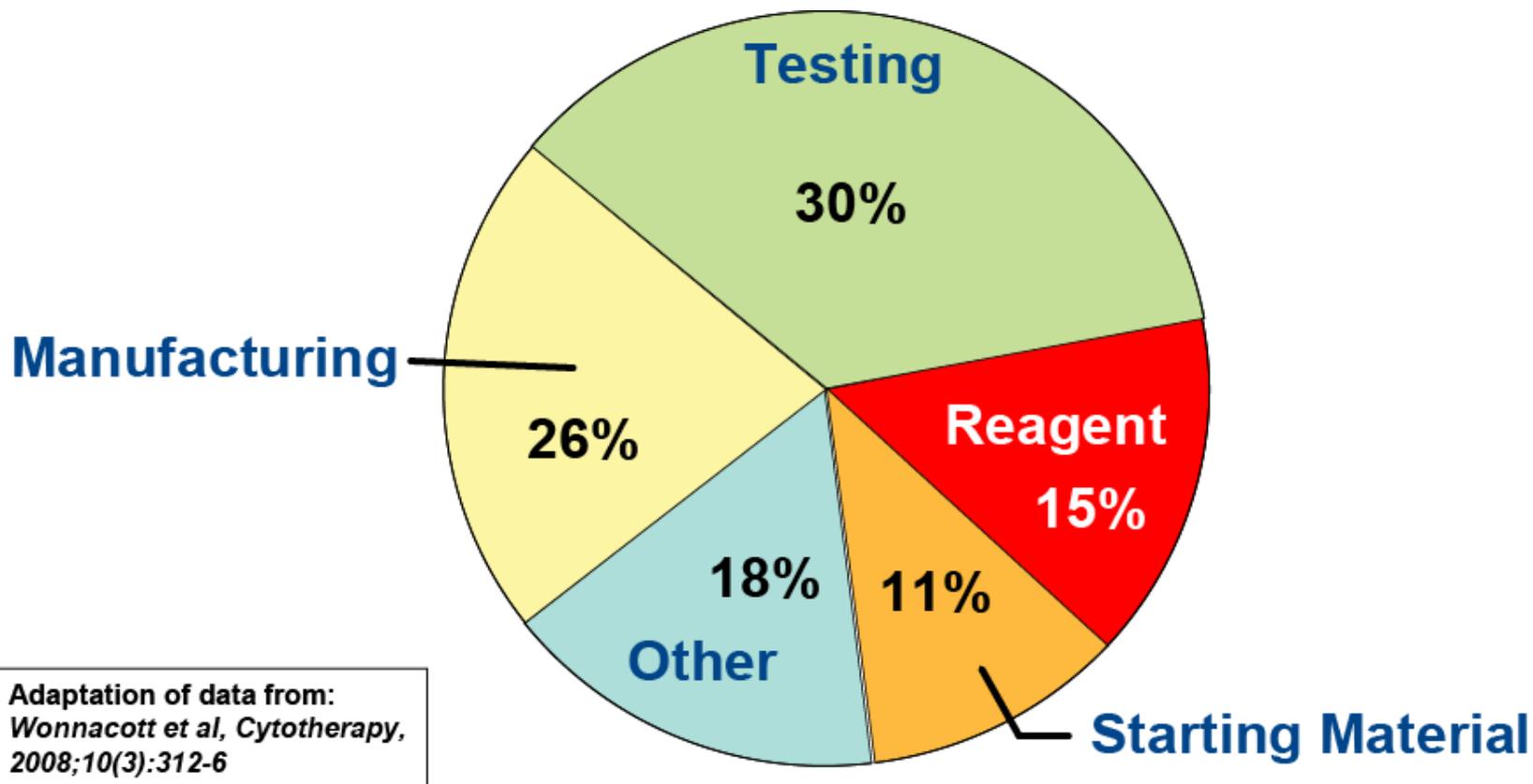
# Stages of Product Development

IND Submission

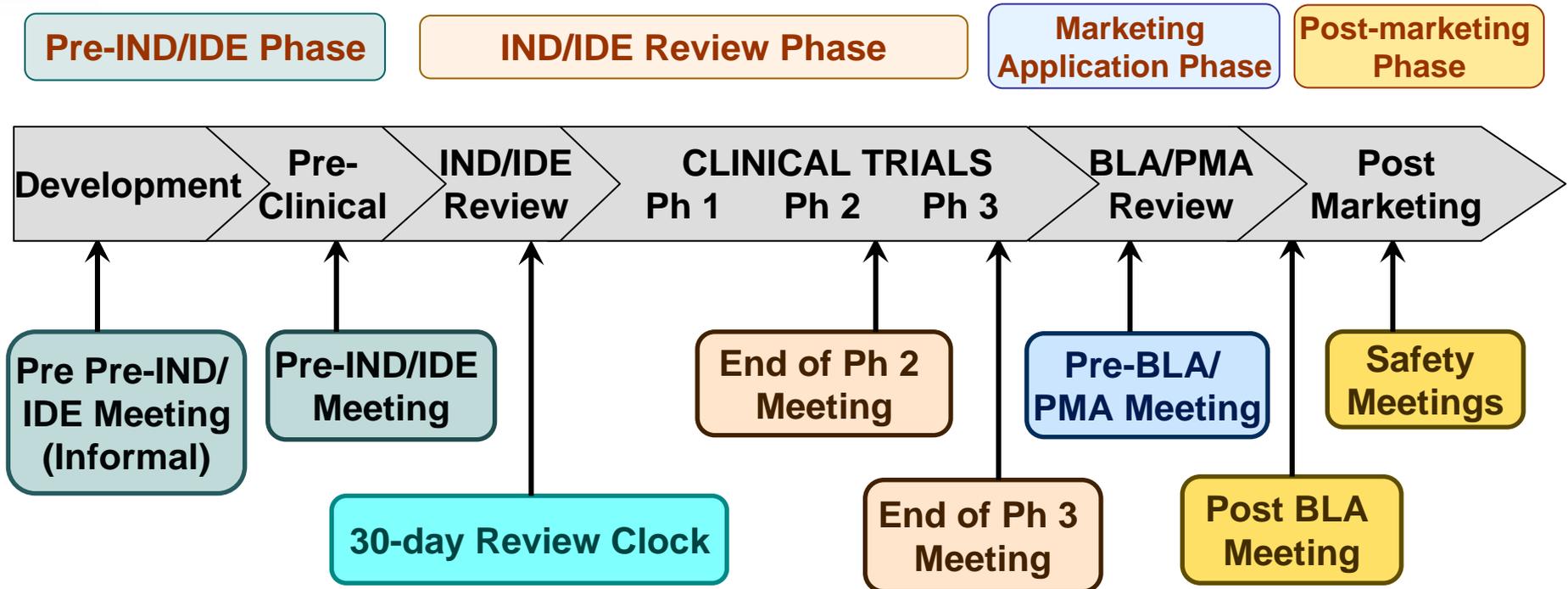


Stage of product development serves to determine key review issues, with safety being a primary focus during all stages of development/clinical testing.

# CMC Issues Typically Resulting in an IND Going on Clinical Hold



# Opportunities for FDA Interaction



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



# Early Interaction with FDA

- Informal – Pre-pre IND, Non-Binding Discussion: Generally CMC and Preclinical Topics, No Minutes Generated
- Pre-IND / Type B – Formal Meeting, Minutes Generated, Non-Binding Recommendations
  - ◆ Sponsors and CBER/FDA staff discuss product development activities prior to submission of an Investigational New Drug application (IND): may touch on CMC, Preclinical and Clinical topics
  - ◆ Represents a key juncture in the regulatory process
  - ◆ **Rule of Thumb:** Generally grant one Type B / pre-IND meeting prior to the submission of an IND: Exceptions do occur when circumstances dictate. Follow-up communication/ interaction is not uncommon

# ■■■ “Right Time” to Request a Pre-IND Meeting: CMC Perspective

- Directly correlated with the maturity of your cellular product development efforts
- Should have developed standard procedures that allow for reproducible product manufacturing: adequate cellular product characterization

# ■■■ Take-Home Messages

- The CMC section of your IND submission should include sufficient information to permit assessment of the potential risks to subjects posed by the proposed clinical studies.
- A summary of the information expected in the CMC section of an IND for an investigational cellular product may be found in available published guidance.
- Early interaction with FDA is encouraged during product development to facilitate preparation of the IND submission.



# Additional CBER Guidance: Composition of IND CMC Section

## **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)**

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078694.pdf>

## **Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product**

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092272.pdf>

## **Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications**

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm202439.pdf>



# ■■■ Contacting the Center for Biologics

## CBER CONTACT INFORMATION

- ▶ PHONE: 1-800-835-4709 (Within U.S.)  
301-827-1800 (Local or Outside U.S.)
- ▶ INTERNET: <http://www.fda.gov/BiologicsBloodVaccines/default.htm>
- ▶ Send e-mail to: [OCOD@fda.hhs.gov](mailto:OCOD@fda.hhs.gov)
- ▶ **OCTGT Regulatory and Administrative Contact:**  
**Patrick Riggins, Ph.D.** (Regulatory Project Manager)  
E-Mail: [patrick.riggins@fda.hhs.gov](mailto:patrick.riggins@fda.hhs.gov) / Phone: 301-827-5366
- ▶ CBER Regulatory and Guidance Documents on the Internet  
at:  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>

