



# **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 CDER, Office of Medical Policy  
and  
The Duke University School of Medicine*



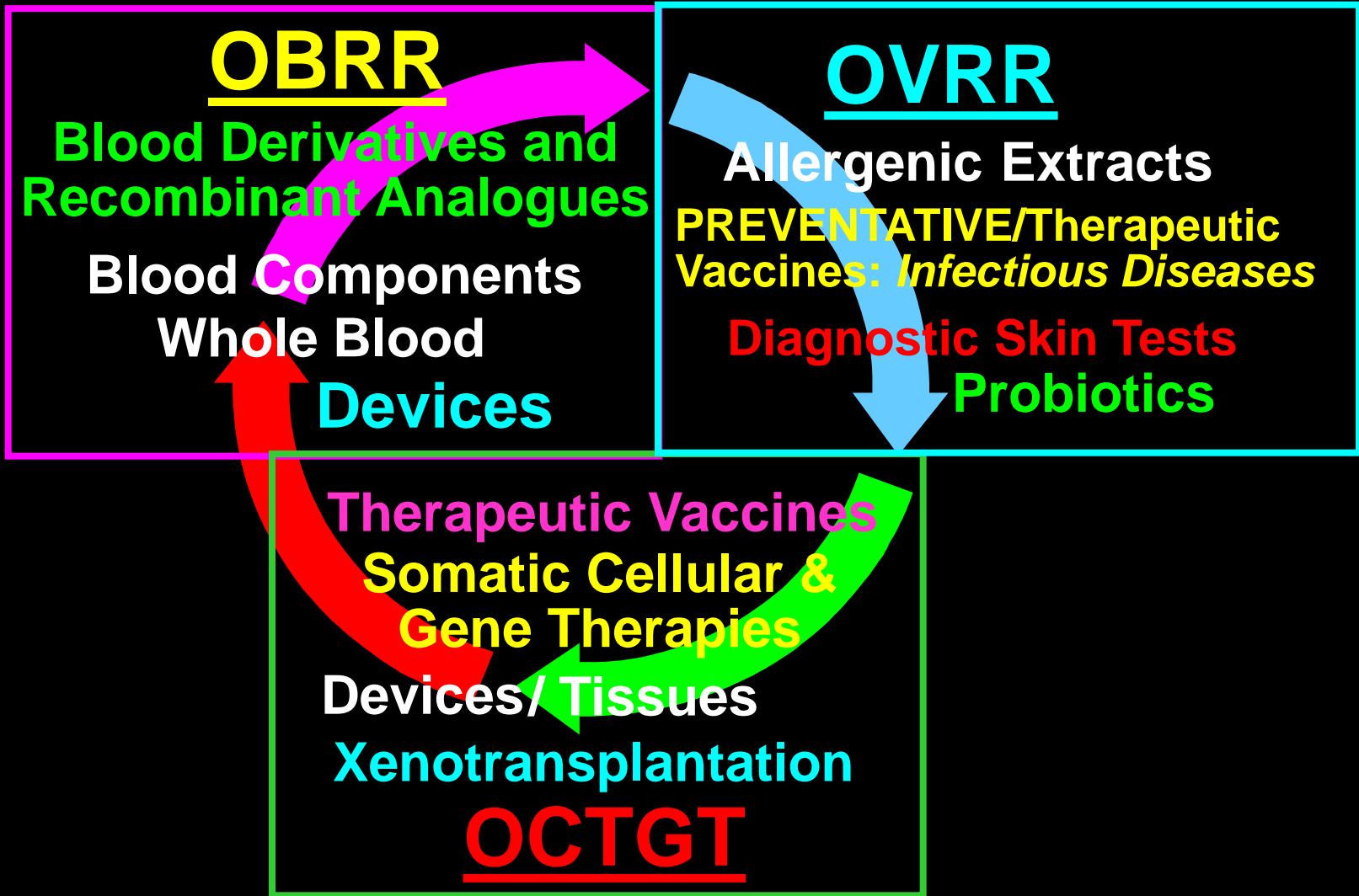
**FDA**

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)

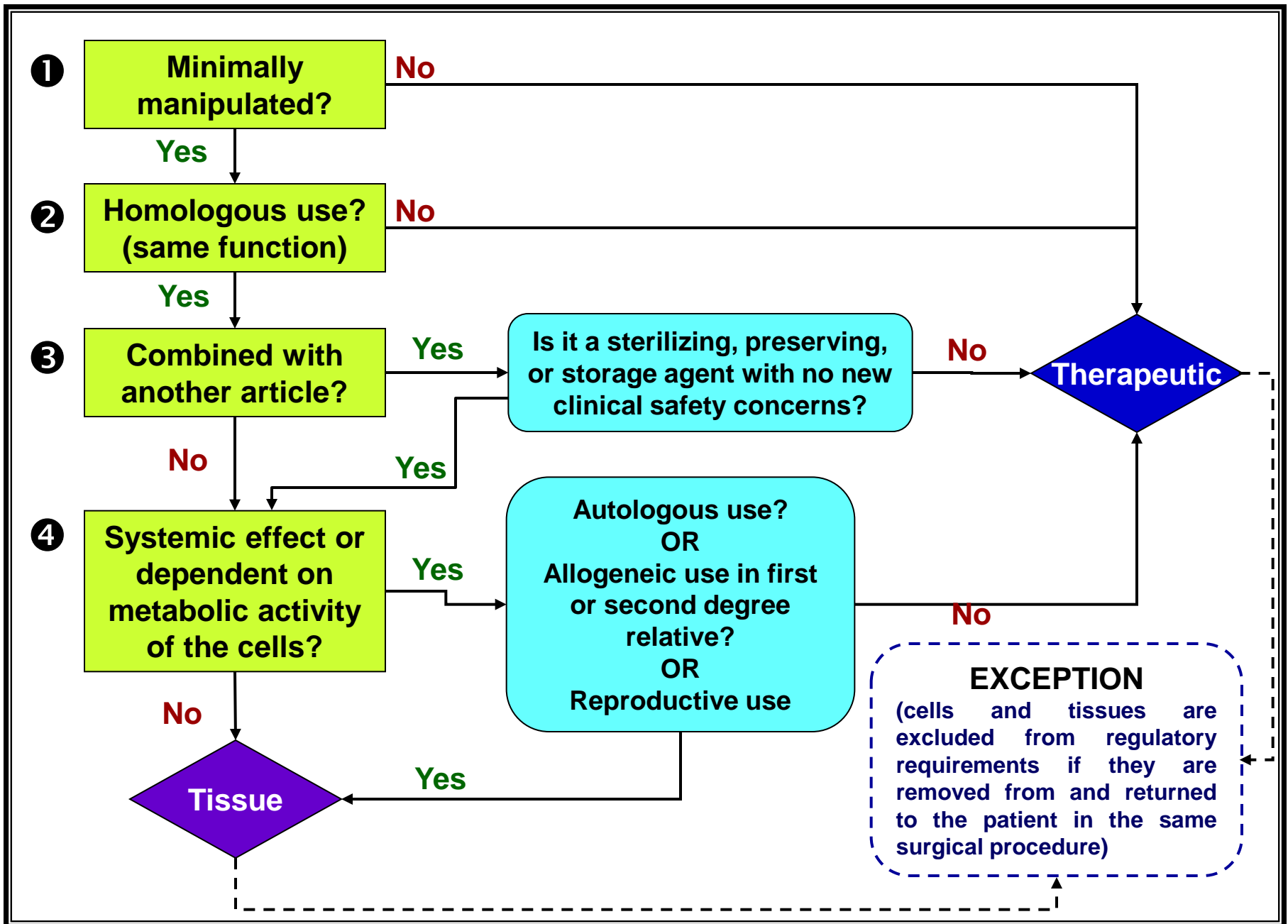
**HCT/Ps may be eligible for regulation as tissues solely under Section 361 of the PHS Act and 21 CFR § 1271**



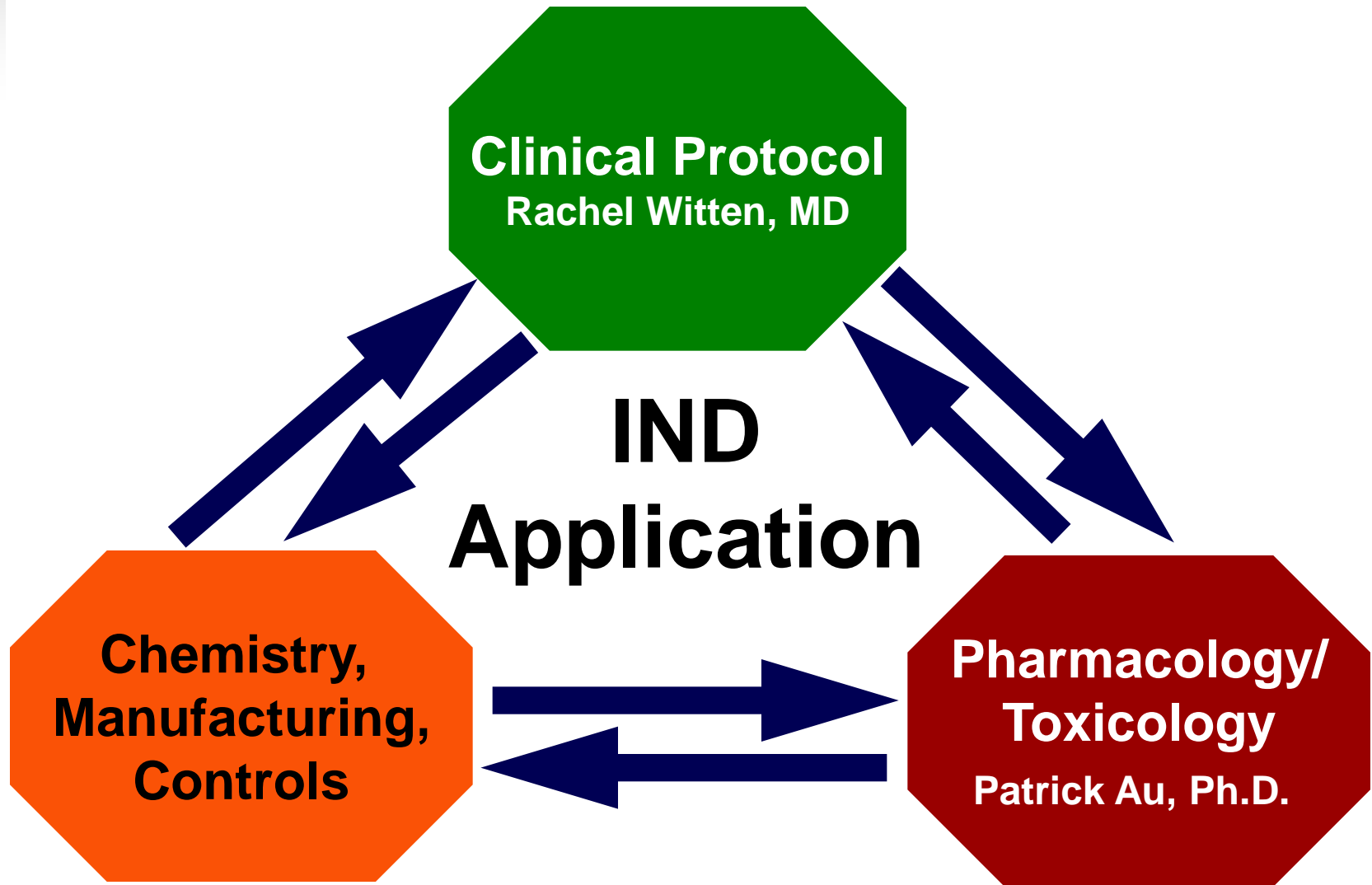
# HCT/P Regulation Solely Under Section 361 and 21 CFR 1271

**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.



# 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 (including environmental assessment</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)
<input type="checkbox"/>	Biosimilar User Fee Cover Sheet	Form FDA 3792
<input type="checkbox"/>	Clinical Trials Certification of Compliance	Form FDA 3674



# 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 method specified in 21 CFR 610.12 or indicate if using alternative test method(s) – *Draft Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products*  
(<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072612.htm>)
- ➔ **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 the 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.



# Cord Blood Regulation

- Cord blood stored for potential future use by a patient unrelated to the donor meets the definition of a “drug” (FD&C Act) and a “biologic product” (PHS Act).
- License granted based on demonstration that recommendations in FDA guidance document applicable to regulatory requirements for a license application are met:

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**Guidance for Industry:** Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications



<b>Product Attributes</b>	<b>Testing</b>	<b>Sample (Type and Timing)</b>	<b>Results of Product Testing</b>
<b>Safety</b>	Infectious diseases – Testing required (21 CFR 1271.45 through 1271.90)	Maternal peripheral blood obtained within 7 d of cord blood collection –Type and timing required (21 CFR 1271.80(a), (b))	All tests neg except non-treponemal test for syphilis when confirmatory test is neg (CMV results are recorded)
			CMV - Report
	Sterility: Bacterial and fungal -Testing required (21 CFR 211.165(b), and 21 CFR 610.12)	HPC-C (pre-cryopreservation)	No growth
	Hemoglobin	Cord blood or donor sample obtained at time of cord blood recovery	No homozygous hemoglobinopathy
<b>Purity and Potency</b>	Total nucleated cells (TNC)	HPC-C (pre-cryopres)	$\geq 5.0 \times 10^8$ TNC/unit HPC-C
	Viable nucleated cells	HPC-C (pre-cryopres)	$\geq 85\%$ viable nucleated cells
	Viable CD34+ cells (flow)	HPC-C (pre-cryopres)	$\geq 1.25 \times 10^6$ viable CD34+ cells/unit HPC-C
<b>Identity</b>	HLA Typing	Cord blood	Report
	Confirmatory HLA typing	Attached segment	Confirms initial
	ABO and Rh Type	Cord blood	Report





## 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.



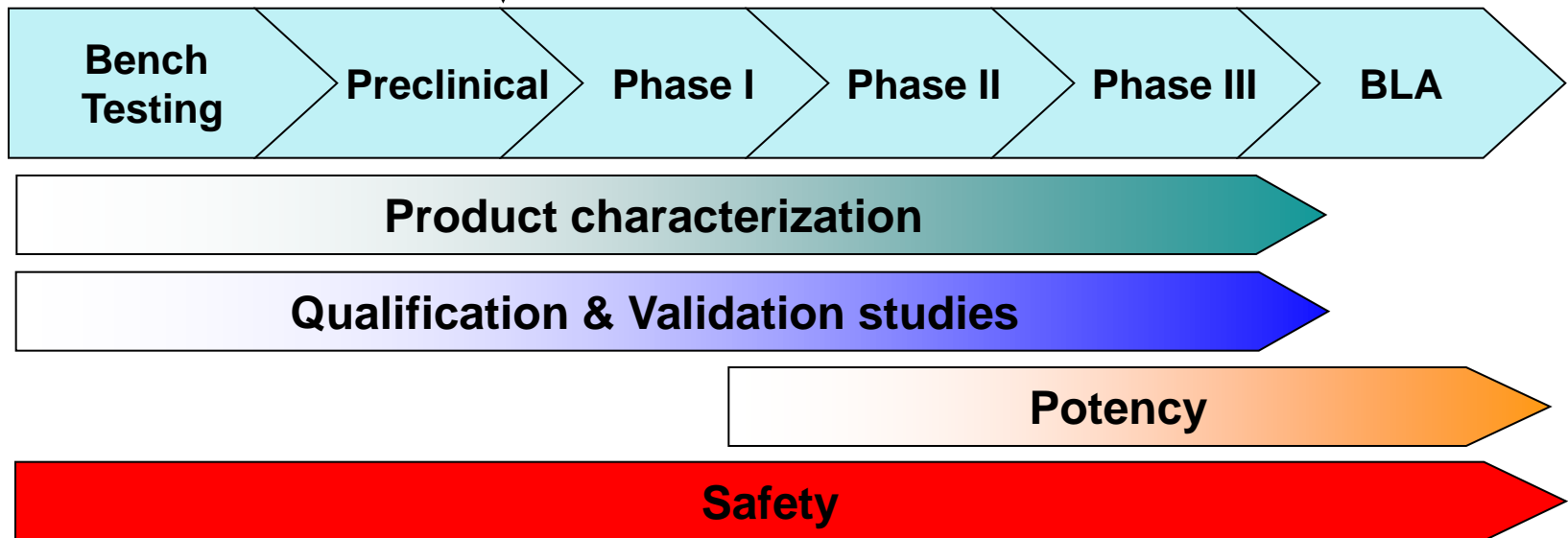
## V. OTHER ISSUES (3)

- **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

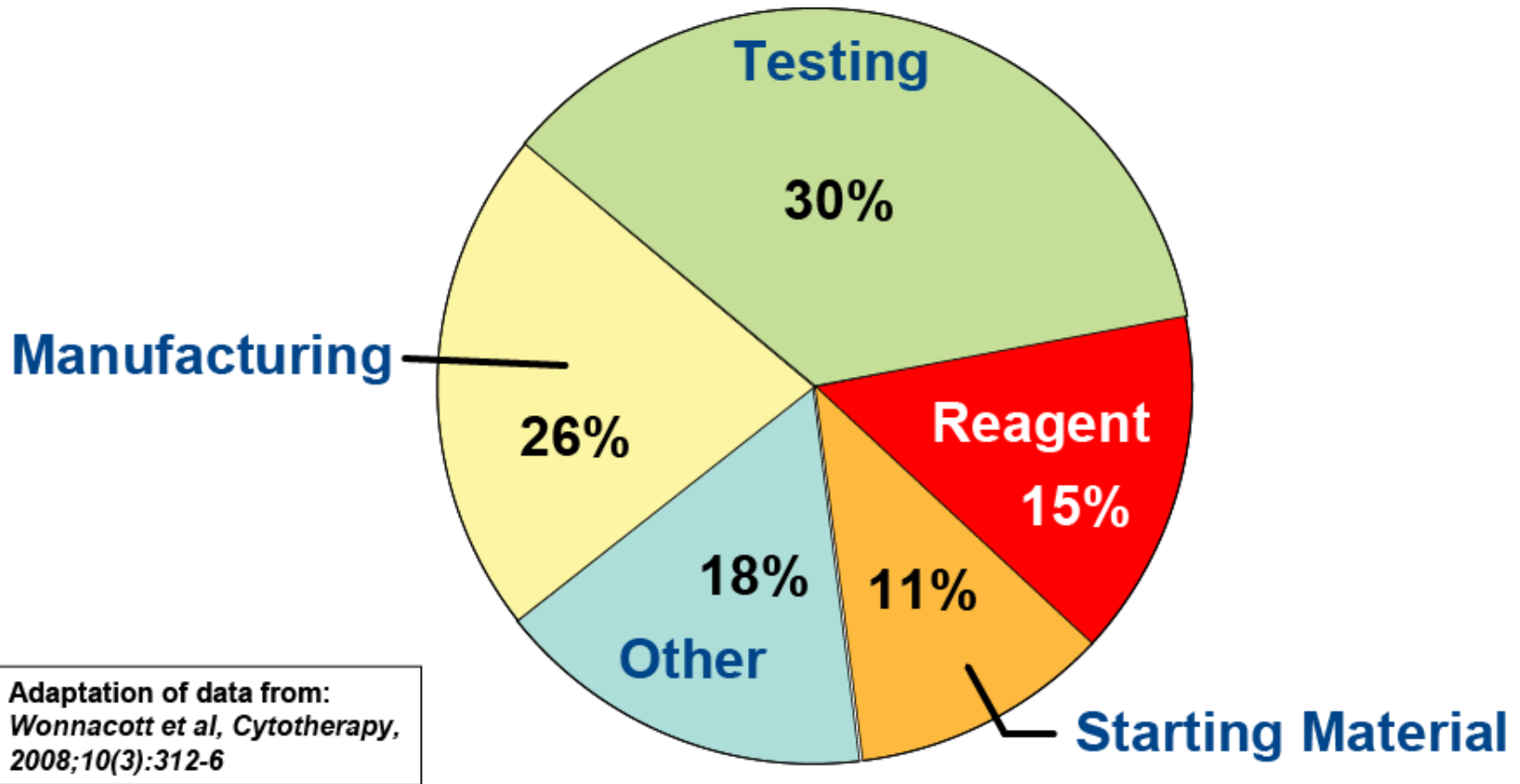
# Stages of Product Development

IND Submission



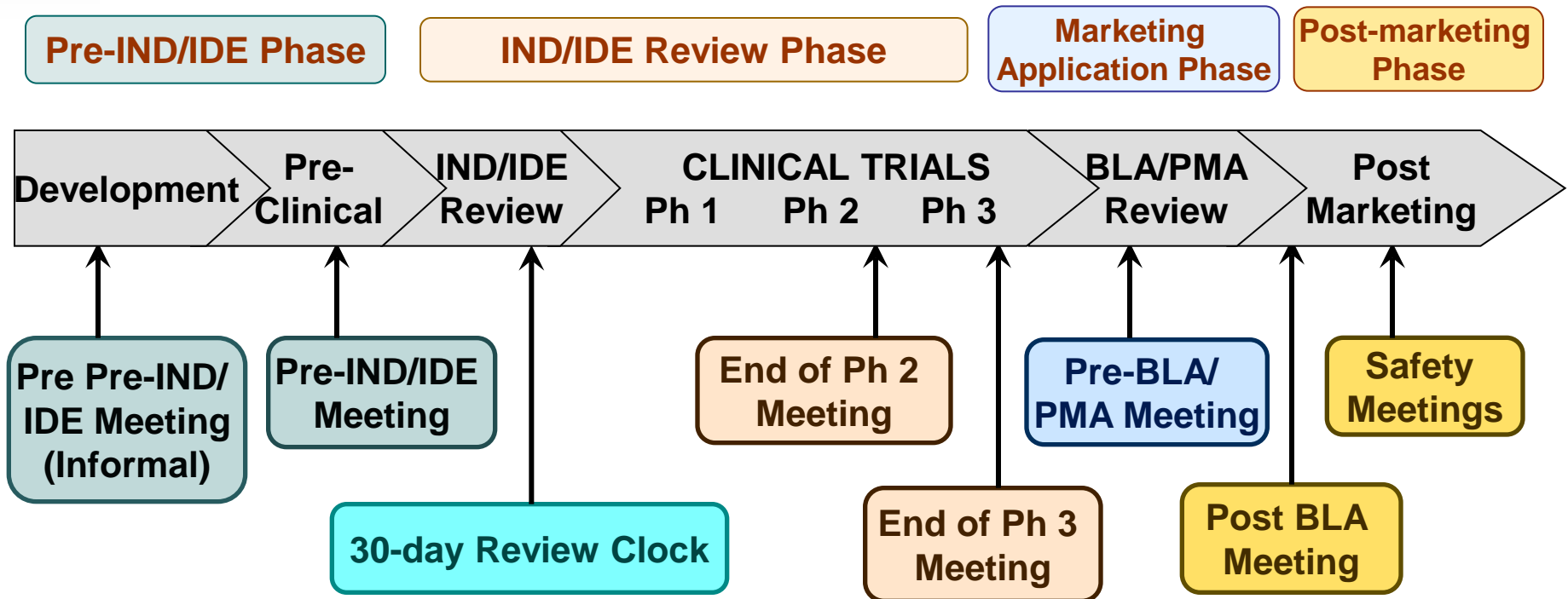
Stage of product development serves to determine key review issues, with safety being a primary focus during all stages of development/clinical testing.

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



Adaptation of data from:  
*Wonnacott et al, Cytotherapy,*  
*2008;10(3):312-6*

# 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

- Determined by 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 regarding product manufacturing, release testing and characterization 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.

# ■■■ OCTGT Contact Information

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## Regulatory Questions:

Contact the Regulatory Management Staff in OCTGT at [CBEROCTGTRMS@fda.hhs.gov](mailto:CBEROCTGTRMS@fda.hhs.gov) or [Lori.Tull@fda.hhs.gov](mailto:Lori.Tull@fda.hhs.gov), or by calling (301) 827-6536

## OCTGT Learn Webinar Series:

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





# Public Access to CBER

CBER website:

<http://www.fda.gov/BiologicsBloodVaccines/default.htm>

Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)

Email: [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)

Phone: 301-827-3821

Manufacturers Assistance and Technical Training Branch  
(MATTB)

Email: [industry.biologics@fda.gov](mailto:industry.biologics@fda.gov)

Phone: 301-827-4081

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