

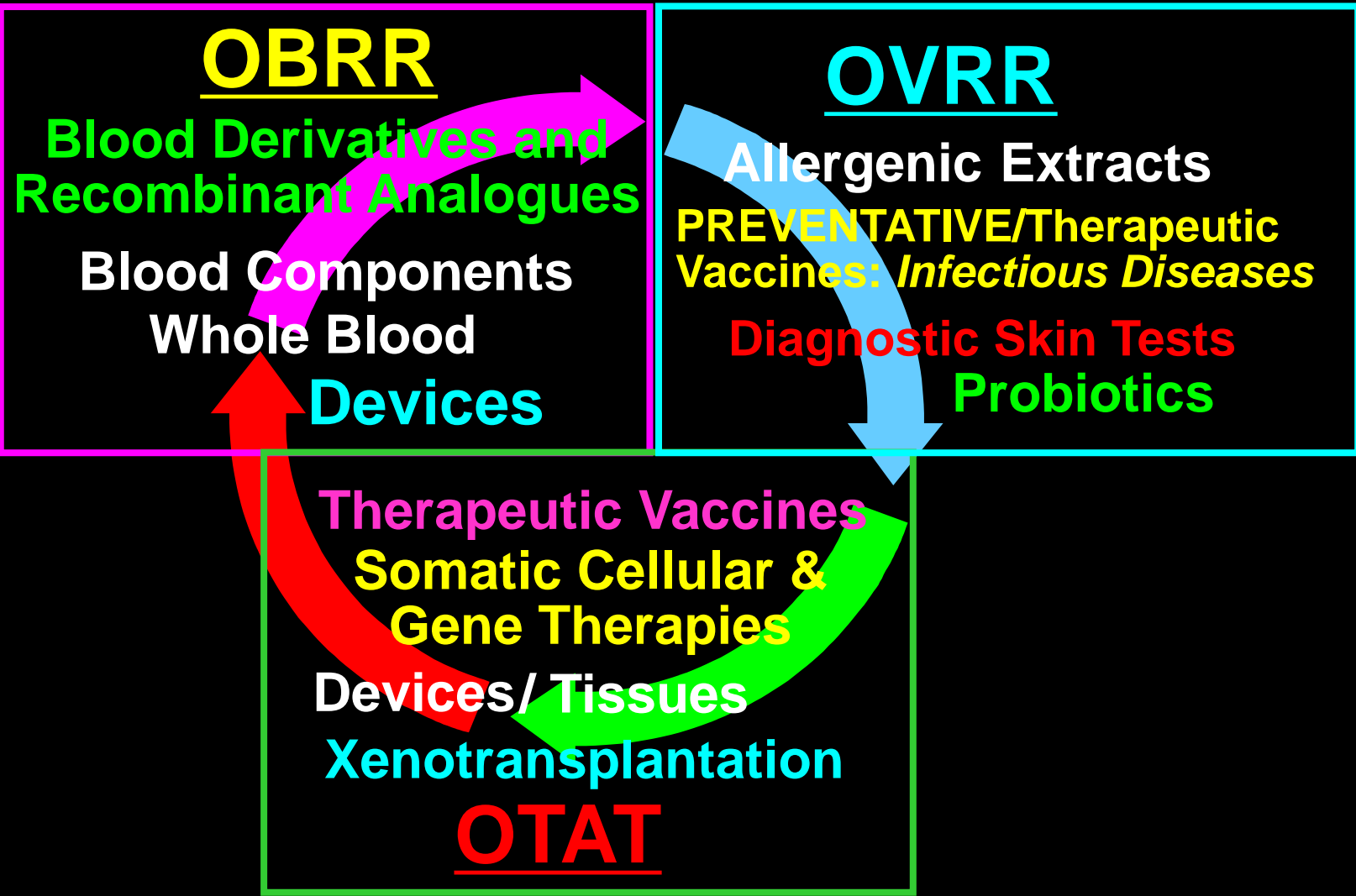
Preparing an IND Application: CBER Breakout Session

Donald W. Fink, Jr., Ph.D.

Division of Cellular and Gene Therapies
Office of Tissue and Advanced Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration

FDA Clinical Investigator Training Course
November 15, 2018

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 21CFR § 1271

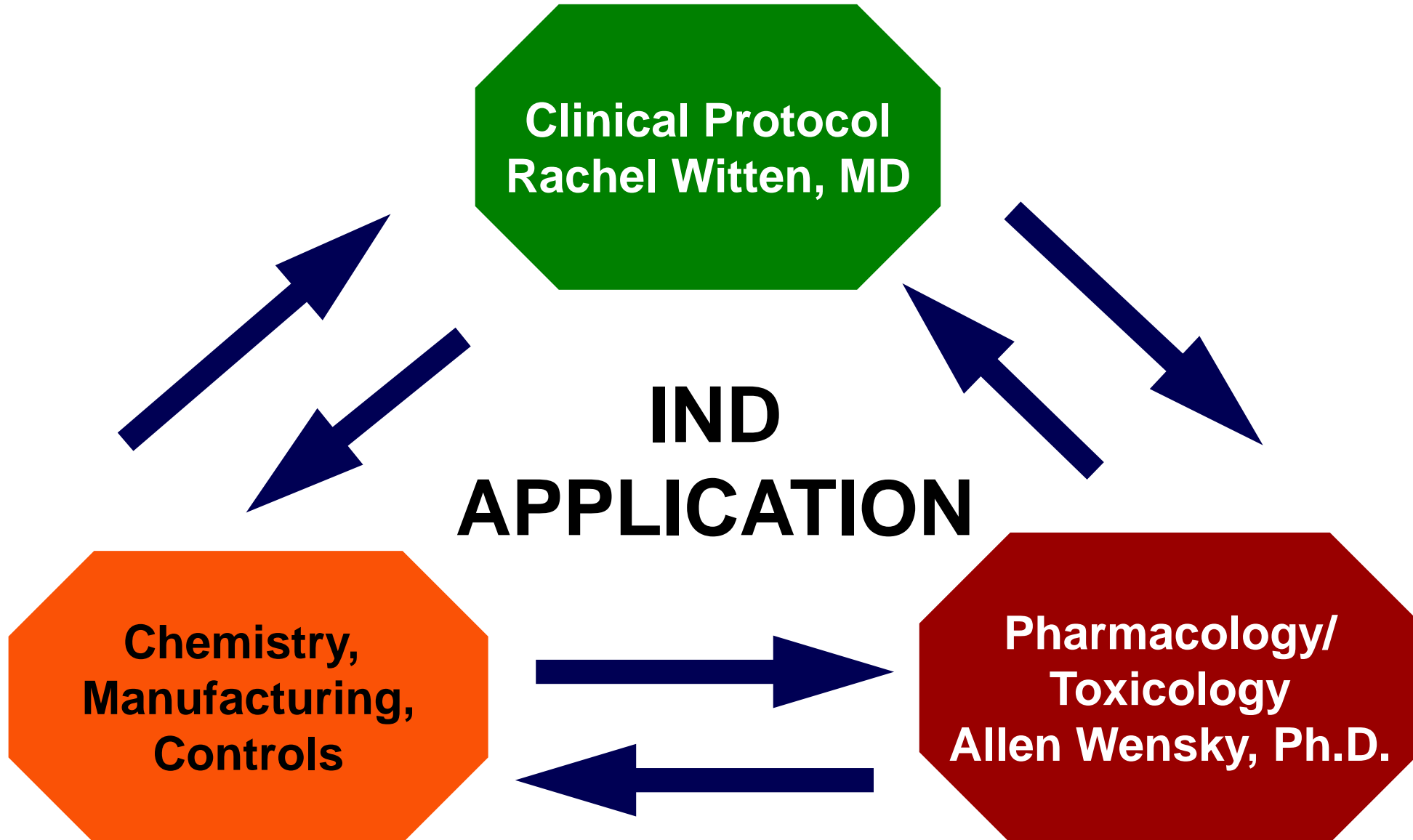
HCT/P Regulation Solely Under Section 361 and 21 CFR 1271



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 | <i>21 CFR 312.23(a)(1)</i> |
| <input type="checkbox"/> | Table of Contents | <i>21 CFR 312.23(a)(2)</i> |
| <input type="checkbox"/> | Introductory statement and general investigational plan | <i>21 CFR 312.23(a)(3)</i> |
| <input type="checkbox"/> | Investigator's brochure | <i>21 CFR 312.23(a)(5)</i> |
| <input type="checkbox"/> | Protocols | <i>21 CFR 312.23(a)(6)</i> |
| <input checked="" type="checkbox"/> | Chemistry, manufacturing, and control data (including environmental assessment) | <i>21 CFR 312.23(a)(7)</i> |
| <input type="checkbox"/> | Pharmacology and toxicology data | <i>21 CFR 312.23(a)(8)</i> |
| <input type="checkbox"/> | Previous human experience | <i>21 CFR 312.23(a)(9)</i> |
| <input type="checkbox"/> | Additional information | <i>21 CFR 312.23(a)(10)</i> |
| <input type="checkbox"/> | Biosimilar User Fee Cover Sheet | <i>Form FDA 3792</i> |
| <input type="checkbox"/> | Clinical Trials Certification of Compliance | <i>Form FDA 3674</i> |

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.

Harnessing the Manufacturing Process



**Chemistry,
Manufacturing,
Controls**



Helpful Reference: Preparing CMC Section for Cell-based Product IND



Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (April 2008)

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/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

CMC Guidance: Information to Include in IND Submission (cont.)



II. PRODUCT RELEASE TESTING/RESULTS

● Microbiological Testing

- ➔ **Sterility Testing (Bacterial/Fungal):** Performed in accordance with requirements outlined in 21 CFR 610.12.
 - ✓ Sterility test appropriate to material being tested, does not interfere or hinder the test.
 - ✓ Test must be validated to demonstrate capability to reliably and consistently detect presence of viable, contaminating microorganisms.
- ➔ **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

CMC Guidance: Information to Include in IND Submission (cont.)



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)

CMC Guidance: Information to Include in IND Submission (cont.)



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.

CMC Guidance: Information to Include in IND Submission (cont.)



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.

CMC Guidance: Information to Include in IND Submission (cont.)



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.

CMC Guidance: Information to Include in IND Submission (cont.)



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)

CMC Guidance: Information to Include in IND Submission (cont.)



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.

- **Product 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.

CMC Guidance: Information to Include in IND Submission (cont.)



V. OTHER ISSUES (3)

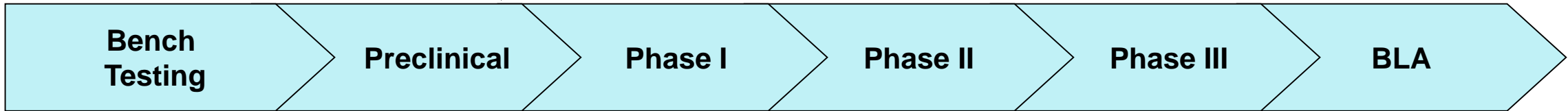
- **Lot-to-Lot Comparability**

- ➔ 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

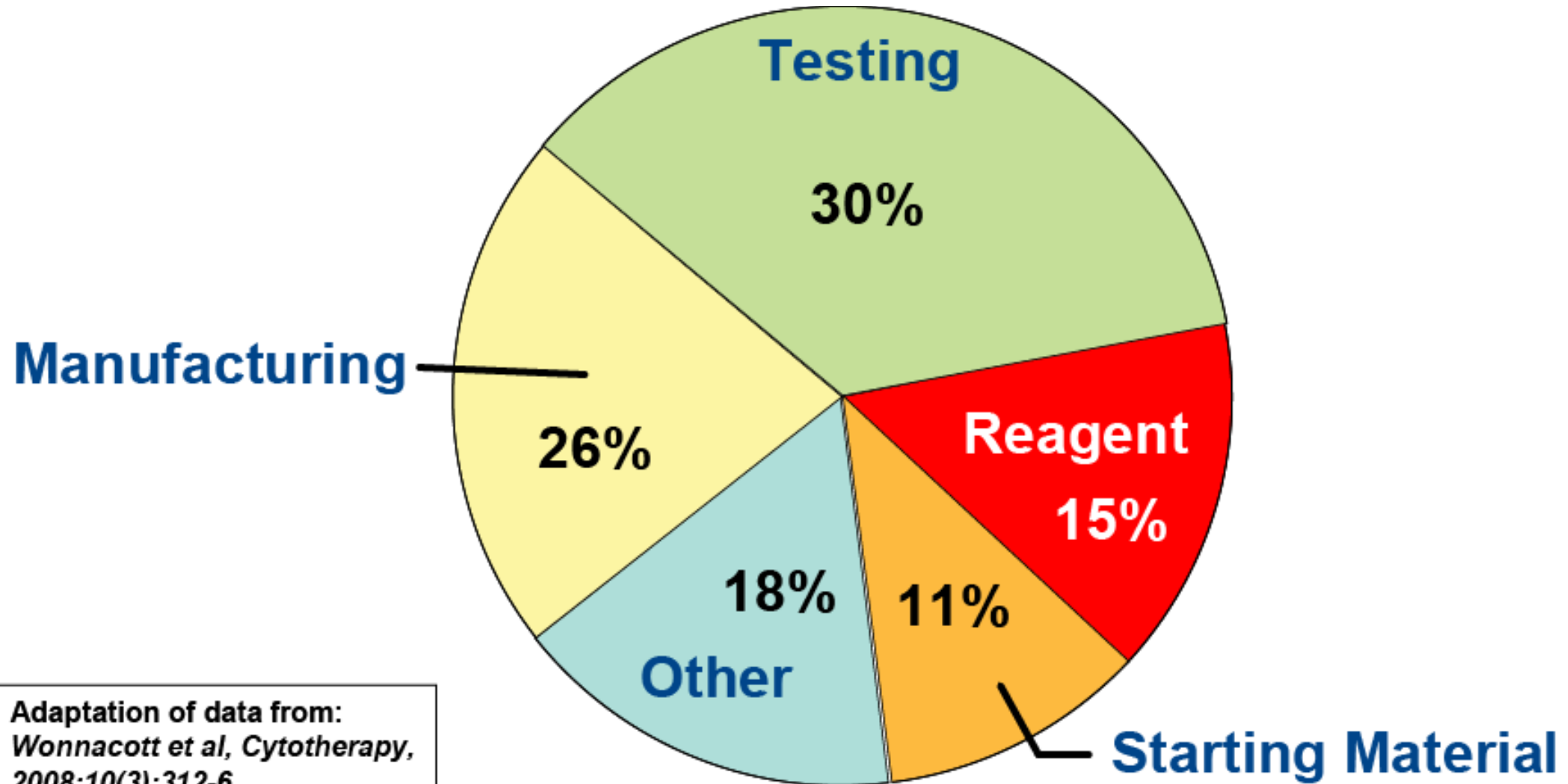


IND Submission



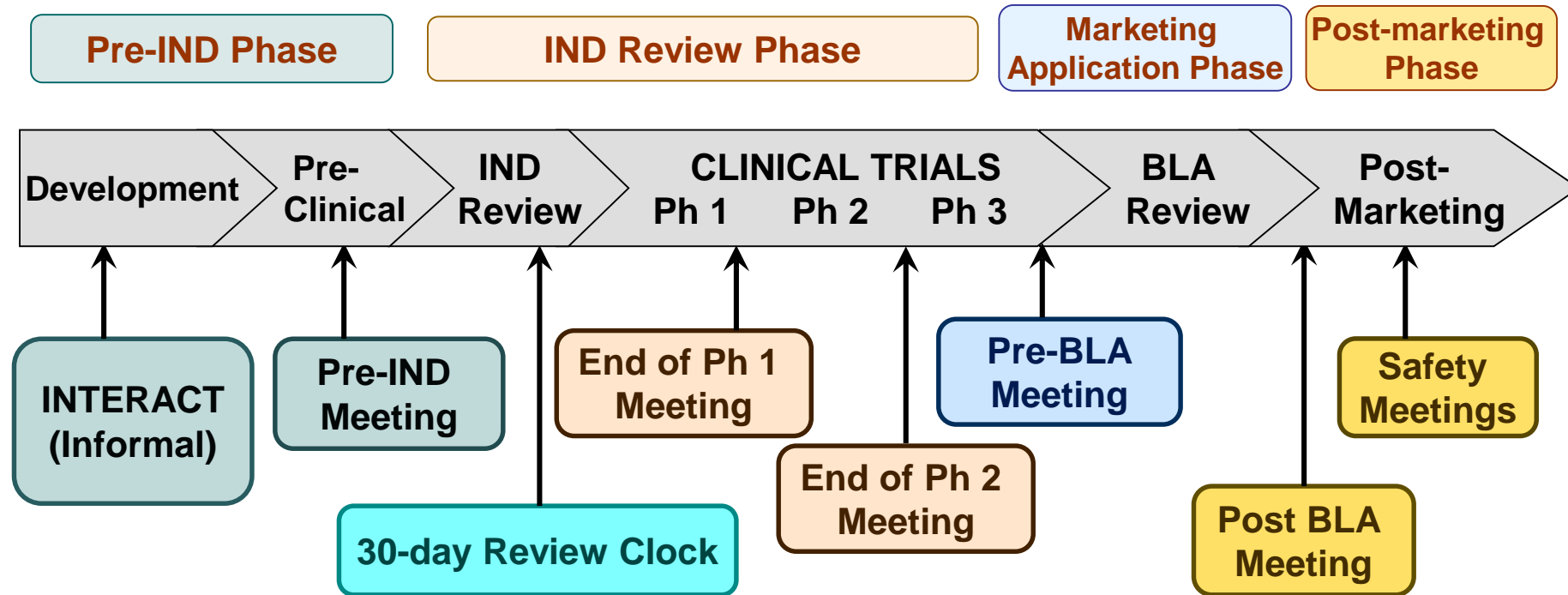
Stage of product development serves to determine key review issues, with safety being a primary focus during all stages of development/clinical testing.

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 that may involve multiple FDA and sponsor interactions

Early Interaction with FDA



- **INTERACT** (Initial Targeted Engagement for Regulatory Advice on CBER Products): Informal, Non-Binding Discussion: Generally CMC and Preclinical Topics, No Minutes Generated

Website:

<https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm>

- **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 development to facilitate preparation of the IND submission, especially for particularly innovative products.

Contact Information

- **Donald W. Fink, PhD**
Donald.Fink@fda.hhs.gov
- **Regulatory Questions:**
OTAT Main Line: 240-402-8190
Email: OTATRPMS@fda.hhs.gov and
Lori.Tull@fda.hhs.gov
- **OCTGT/OTAT Learn Webinar Series:**
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>
- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone: 1-800-835-4709 or 240-402-8010**
- **Consumer Affairs Branch:** ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch:**
industry.biologics@fda.gov
- **Follow us on Twitter:** <https://www.twitter.com/fdacber>



FDA Headquarters
Federal Research Center at White Oak
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002



Putting Together Your IND Submission (CBER): Preclinical Considerations

Allen Wensky, Ph.D.

Center for Biologics Evaluation and Research (CBER)

Office of Tissues and Advanced Therapies (OTAT)

Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)

Pharmacology/Toxicology Branch (PTB)

allen.wensky@fda.hhs.gov

CLINICAL INVESTIGATOR TRAINING COURSE (CITC): SESSION 7: INDs AND IDEs FROM START TO FINISH

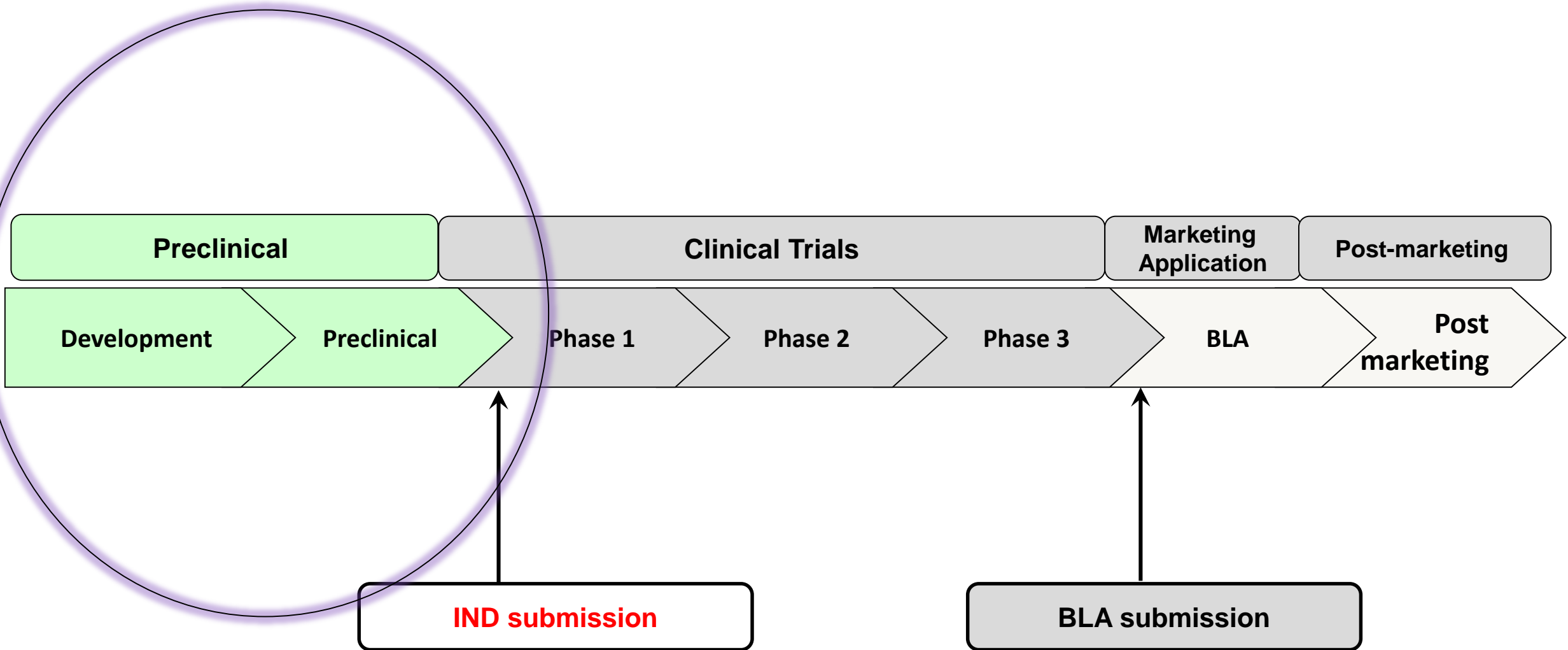
November 15, 2018

Overview



- Preclinical Regulatory Review Principles
- Potential Pitfalls / Regulatory Issues
- Early Interactions
- Resources

Product Lifecycle for Biologics: Focus on the Preclinical Phase



What Regulations Govern Preclinical Testing?

Pharmacology & Toxicology Studies

“...adequate information about the pharmacological and toxicological studies...on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. **The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.**”

IND Regulations [21 CFR 312.23 (a)(8) - Pharmacology and Toxicology]

Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at

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

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2013

- Final Guidance

- Current thinking of the Agency on this topic
- First comprehensive FDA guidance on preclinical assessment of cell and gene therapy (CGT) Products
- Explicitly incorporates 3 R's: recommendations to reduce, refine, and replace animal use in a preclinical program

Expectations from Preclinical Data

- To support a **rationale** for the first-in-human clinical trial
 - For cell and gene therapy products, the trial is usually conducted in the disease population, not in healthy volunteers
- To make **recommendations** regarding the proposed clinical trial
 - Initial safe starting dose, dose-escalation scheme, dosing schedule, organ toxicity, eligibility criteria, clinical monitoring
- To meet **regulatory requirements**
 - 21 CFR 312.23 (a)(8)
 - 21 CFR 58 (Good Laboratory Practice (GLP) compliance)

CBER Review: Product-Based

- No “one size fits all” regulatory approach
- Data necessary to support development depends on the characteristics of the product
- Preclinical studies are designed to support use of a specific product for a specific clinical indication.
- Review approach is based on balancing risk and benefit.





Sources of Data to Support an IND

- GLP-compliant toxicology studies conducted by a certified testing facility
- Well-controlled studies conducted in house
- Published data in peer-reviewed journals
- Cross-reference to similar products in previously submitted files to FDA
- Detailed clinical study reports from clinical trials

Preclinical Expectations for Early Phase Clinical Trials

- Potential mechanism of action (e.g., targeted killing, anti-tumor, tolerance induction)
- Establish pharmacologically effective dose(s)
- Optimize route of administration (ROA) / dosing regimen
- Establish rationale for species / model selection

Preclinical Expectations for Early Phase Clinical Trials

- Establish a dosing scheme
- Potential target tissue(s) of toxicity / activity
- Parameters to monitor clinically
- Eligible patient population

Preclinical Study Design(s)

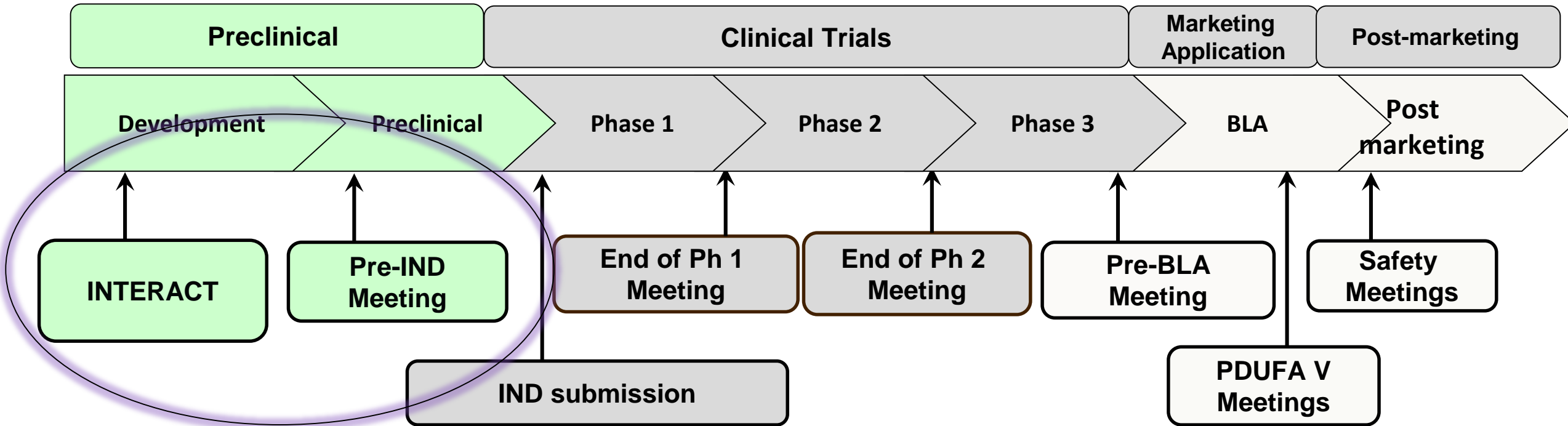
- Assess pharmacology / proof-of-concept (POC) / vector distribution / cell fate in relevant animal model(s) of disease / injury, as feasible
- Assess safety / toxicology (T) / vector distribution / cell fate in healthy animals
- Hybrid pharmacology-toxicology study design
 - POC + T + product fate – incorporate activity and safety endpoints in an animal model of disease / injury
 - Local microenvironment and pathophysiology status of the model may impact the safety / bioactivity of the product

Considerations for Appropriate Animal Species / Model



- There is no 'default' to the use of nonhuman primates
- There is no 'default' to the use of both a rodent and a non-rodent species
- There is no 'default' to the use of multiple species
- **Understand the limitations of the species / model(s) used**
- **Scientific justification should be provided for the animal species / model(s) used**

Opportunities for Interaction - Preclinical Development





Early Communication with OTAT: *INTERACT**

- **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s (*previously known as pre-pre-IND interactions*)
- **Goal:** *To obtain early feedback on a product development program for a novel investigational agent*
- **Purpose**
 - A mechanism for early communication with OTAT
 - Non-binding, informal scientific discussions with CBER/OTAT review disciplines
 - Initial targeted discussion of specific issues
 - *Primary contact:* INTERACT-CBER@fda.hhs.gov

*<https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm>

Pre-IND Meeting: Preclinical

- **Preclinical**
 - **A comprehensive summary of all completed preclinical studies** (*in vitro* and *in vivo* studies, animal species/models, study designs, product manufacturing and formulation, resulting data and interpretation)
 - **Discussion of the planned preclinical program** (e.g., animal species/models, product manufacturing and formulation, study designs, ‘Animal Rule’ issues, etc.)

Do's for INTERACT and Pre-IND Meetings [Preclinical Perspective]

- Do read and understand FDA/ICH Guidances, regulations, etc. before meeting with FDA
- Do include the preclinical development plan
- Do specify similarities and differences between the preclinical and clinical products
- Do specify similarities and differences between the preclinical and clinical delivery devices/procedures
- Do include the design of your completed and proposed preclinical studies
- Do make the package reader-friendly



Don'ts for INTERACT and Pre-IND Meetings [Preclinical Perspective]

- Don't conduct the definitive preclinical studies without seeking input from CBER/OTAT
- Don't forget to discuss the limitations for each test system used
- Don't forget to consider new *in vitro* and *in vivo* test models as the science and technology progress
- Don't forget that the preclinical testing program may need to be adapted to the specific cell therapy product and level of risk



Summary



- It is important to keep FDA / CBER / OTAT involved at an early phase of the product development program
- The preclinical study designs should be supported by scientific rationale / data
- Novel therapies mean novel testing paradigms

Selected Guidances

- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM329861.pdf>
- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM359073.pdf>
- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (October 2011)
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM278673.pdf>

Contact Information



- **Allen Wensky**
allen.wensky@fda.hhs.gov
- **Regulatory Questions:**
OTAT Main Line – 240 402 8190
Email: OTATRPMS@fda.hhs.gov and
Nannette.Cagungun@fda.hhs.gov



FDA Headquarters

- **OTAT Learn Webinar Series:**
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>
- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch:** ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch:** industry.biologics@fda.hhs.gov
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Putting Together Your IND Application (CBER): Clinical Considerations

Rachel Witten, M.D.

Center for Biologics Evaluation and Research (CBER)

Office of Tissues and Advanced Therapies (OTAT)

Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)

CLINICAL INVESTIGATOR TRAINING COURSE 2018 (CITC): SESSION 7: INDs AND IDEs FROM START TO FINISH

November 15, 2018

Overview



- What is an IND?
- When do you need an IND?
- Who can apply for an IND?
- What should an IND contain?
- How does FDA review an IND?
- Expectation for a First-in-Human Study

Investigational New Drug application

- 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 (21CFR312) outline requirements

- Use of Investigational drug
- Submission of application to FDA
- Review by FDA

When Do You Need to Submit an IND Application

An IND application is required for:

- ❑ Clinical investigation of a new drug or biologic
- ❑ Change to an existing approved drug or biologic, including a new:
 - Indication or significant labeling or advertising change
 - Dosage form and schedule
 - Route of administration
 - Patient population (e.g., pediatric, gender)

Exemptions From IND Application

Criteria for exemption from the IND regulations (21 CFR 312.2(b))

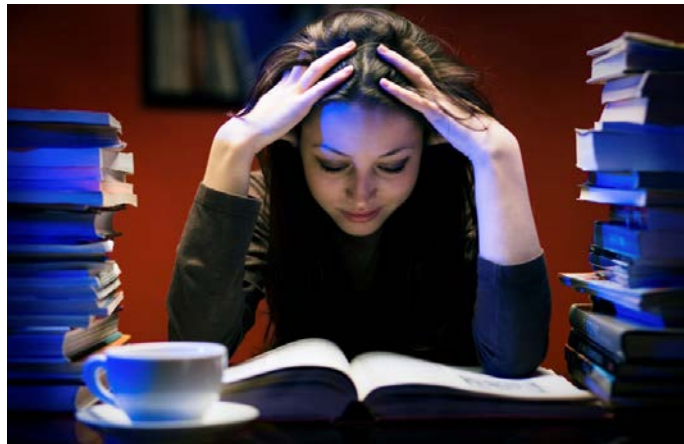
- Drug or biologic product is lawfully marketed in the United States
- No intent to support new use or labeling change
- No intent to support change in advertising
- No new factor --- such as route of administration, dosage, or study population --- that significantly increases risk
- No promotion or representation of product as safe or effective treatment for condition under study

Who can apply for IND application

- IND applicant is called a “**sponsor**”
Sponsor takes responsibility for and initiates a clinical investigation
- IND sponsor may be a company, institution, or an individual
- IND **sponsor-investigator**
An individual who both initiates and conducts the clinical trial

You Have Decided to Submit an IND Application

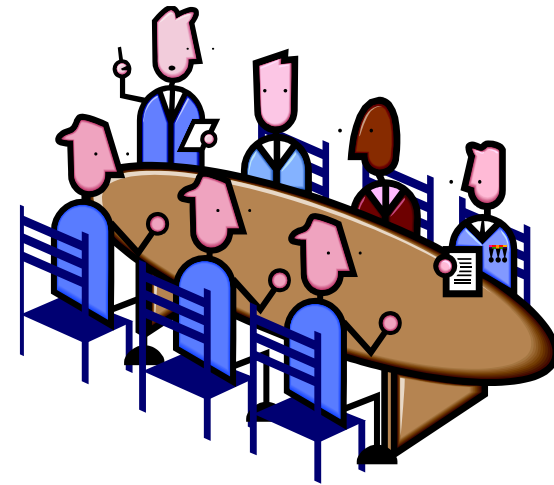
- The time required to prepare an IND will depend on available information on product characterization, extend of pre-clinical data, and any clinical data from relevant studies.
- Study the relevant FDA instructions and forms.
- Determine how your organization can best meet those requirements.



Pre-IND meeting

Highly recommended for new products

- A consultation provided to sponsors and investigators planning to submit an IND application
- This meeting is usually scheduled 3-9 months before the planned IND submission
- Pre-IND package may include:
 - IND product's characteristics
 - manufacturing processes
 - planned or completed pre-clinical studies
 - development plan
 - design of the planned investigation in humans



Please provide specific questions to the Agency about any or all of the above.

Know IND Application's Content and Format

(21 CFR 312.23(a))

- Form 1571 (21 CFR. §312.23(a)(1))
- Table of Contents (21 CFR. §312.23(a)(2))
- Introductory Statement (21 CFR. §312.23(a)(3))
- General Investigational Plan
- Investigator's Brochure (21 CFR. §312.23(a)(5))
- **Clinical Protocols 21 CFR. §312.23(a)(6))**
- Form 1572 (21 CFR. §312.23(a)(6))
- Chemistry, Manufacturing & Control Information (21 CFR. § 312.23(a)(7))
- Pharmacology & Toxicology information (21 CFR. §312.23(a)(8))
- A summary of previous human experience with the investigational product (21 CFR. §312.23(a)(9))
- Additional or relevant Information (e.g., reference to previous submissions)



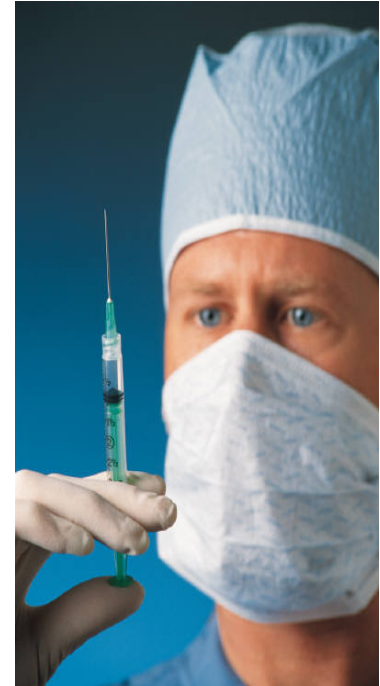
Structure of the FDA Review Team

- Regulatory project manager
- CMC product reviewer
- Preclinical pharm/tox reviewer
- Clinical reviewer
- Biostatistician
- Consultants



IND Application: Protocols 21 CFR 312.23(a)(6)

- ❑ **Phase 1 protocol** may be less detailed
 - Provide all the critical details regarding assessments of safety, including # of patients, dosing plan, safety exclusion criteria, toxicity stopping rules, plan for staggering of subjects, and procedures for safety assessments
- ❑ **Phase 2 and 3 protocols** provide sufficient details
 - Objectives and purposes should be clearly stated
 - The protocol should contain details of the observations and measurements to be made to fulfill the objectives of the trial
 - The protocol should provide a description of clinical procedures, lab tests, and all measures to be taken to monitor the effects of the drug



DON'T forget sufficient descriptions of safety monitoring in your protocol, irrespective of phase of development.

The Procedural Aspects

- Regulatory review and all interactions with an IND sponsor must occur within 30 days of the receipt date:
- Information Requests
- Teleconferences
- Additional data submissions
- Protocol modifications
- By Day 30, the FDA will notify the sponsor that the IND application (studies)

May proceed, OR will be placed on “HOLD”

Understand the Grounds for Imposition of Clinical Hold (21 CFR 312.42)



Phase 1 studies

- Human subjects are exposed to an unreasonable and significant risk of illness or injury
- Clinical investigators are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND application
- Investigator Brochure is misleading, erroneous, or incomplete
- IND application does not contain sufficient information to assess the risks to subjects
- Inadequately described product preparation or formulation
- IND application is for the treatment of a life-threatening or serious disease affecting both genders and only one gender is included in the proposed trial and there are no plans to include both genders in subsequent trials

Phase 2 and 3 studies

- Any of the above, OR
- The protocol is deficient in design to meet its stated objectives



(As far as we know, photo is public domain)

When your IND Could be Release from Clinical Hold

- FDA sends a letter stating the reasons for hold and how to address them
- IND sponsor submits a written response to be reviewed within 30 days
- If the response is adequate, the sponsor is released from hold and the IND application is in effect
- FDA sends a letter stating the study may proceed.



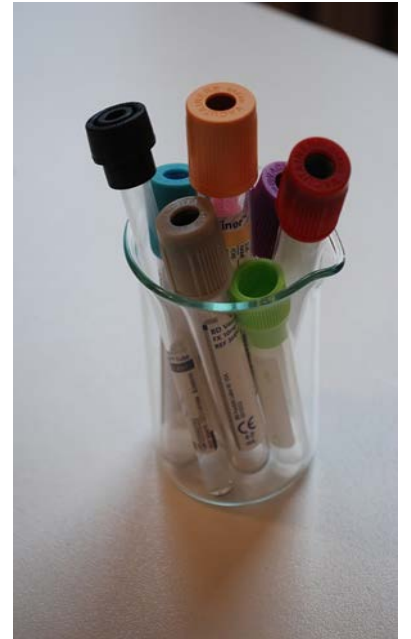
Cell and Gene Therapies: Unique Issues

Complexity of products

- May impose practical limits on dose produced. on the concentration or volume that can be delivered
- Might restrict the range of doses that are feasible

Preliminary assessments of product activity, short-term responses or longer-term outcomes---e.g.,

- Gene expression
- Cell engraftment
- Changes in immune function
- Physiologic responses
- Prospective biomarkers



Cell and Gene Therapies: (cont)

Choice of Study Population



FDA looks at overall risk-benefit for the study population

- Healthy normal subjects are almost never included in trials for cellular and gene therapy products
- Products might have long-term risks or permanent adverse effects

Patients with advanced disease and limited options

- Might be preferred population, if they make the risks acceptable in spite of uncertain benefit
- Might be more vulnerable to complications of adverse reactions, which might increase the risks
- Confounding adverse events due to underlying disease could make safety data difficult to interpret
- Advanced disease state may present irreversible pathology, which may not respond to the experimental therapy

Cell and Gene Therapies: (cont)

Treatment Plan



- Most first-in-human trials of cellular and gene therapies include staggered administration to limit overall risk
- Staggered administration
 - The interval is intended to be long enough to monitor for acute and subacute adverse events
- Cohort size can vary depending on the amount of risk that is acceptable for the indication
- Smaller cohorts might be adequate for a product intended to improve survival
- Larger cohorts may be useful to provide assurance about safety before escalating the dose of a product expected to provide only a modest benefit

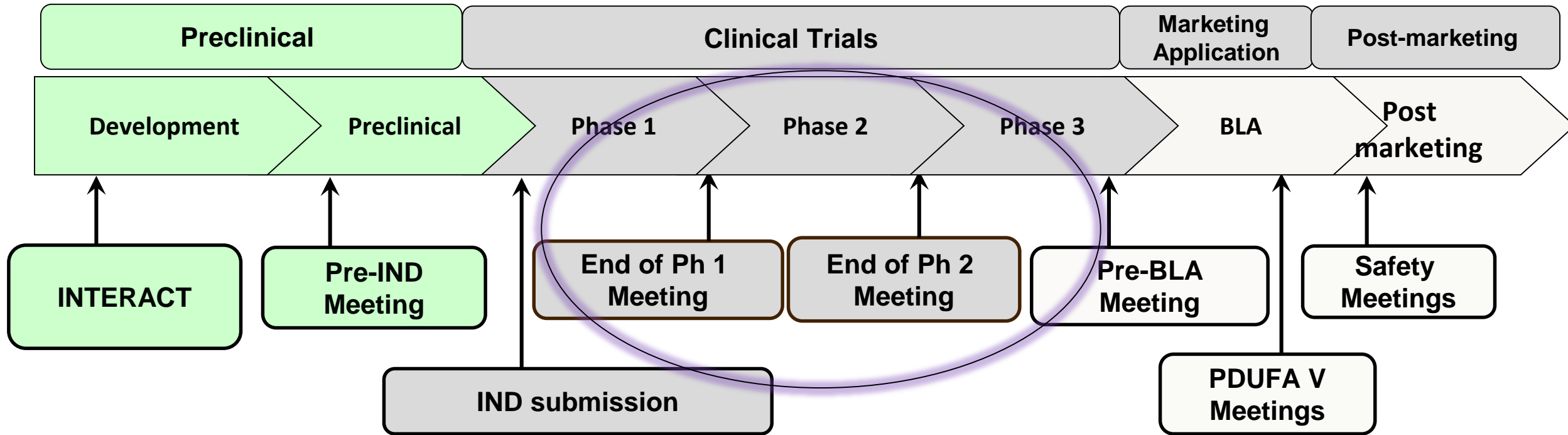


How to avoid problems

dreamstime.com

- **Don't ignore Pre-IND Input from FDA!**
- Create reviewer-friendly IND submission
- Include copy of the protocol, including details of safety monitoring plan
- Provide background information and scientific rationale for your study
- Don't forget to include previous human experience (letter of cross reference)
- Provide your rationale for the dose selection
- Endpoints (primary and secondary)
- Individual and study stopping rules
- Informed Consent and Informal assent forms
- **Be available for any discussion during the first 30 days!**

Opportunities for Interaction - -Clinical Development



CBER Initiatives

Facilitating additional Interactions with FDA

- INTERACT (Initial Targeted Engagement for Regulatory Advice on CBER products)
 - **INTERACT** Meetings Program was created for potential sponsors to engage with CBER staff and obtain advice on a specific topic or issue that is critical to early product development
 - Email: interact-cber@fda.hhs.gov
- RMAT (Regenerative Medicine Advanced Therapy)
 - Sponsors of cell and gene therapies are eligible to obtain an RMAT designation if their product is intended to treat serious or life-threatening diseases and there is preliminary clinical evidence that the product can address unmet medical needs.
 - All benefits of Breakthrough designation: meeting with FDA throughout development, rolling review, intensive guidance on efficient product development beginning as early as Phase 1 and more.

Guidances

- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM359073.pdf>

Three draft Gene Therapy Guidance documents in 2018:

- Treatment of Hemophilia
- Treatment of Retinal Disorders
- Treatment of Rare Diseases

Contact Information

- Rachel Witten, M.D.

Email: rachel.witten@fda.hhs.gov

- Regulatory Questions:

OTAT Main Line – 240 402 8190

Email: OTATRPMS@fda.hhs.gov and

Lori.Tull@fda.hhs.gov

- OTAT Learn Webinar Series:

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

- CBER website: www.fda.gov/BiologicsBloodVaccines/default.htm

- Phone: 1-800-835-4709 or 240-402-8010

- Consumer Affairs Branch: ocod@fda.hhs.gov

- Manufacturers Assistance and Technical Training Branch: industry.biologics@fda.gov

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