FDA's Clinical Investigator Course

Preparing an IND Application: CBER Breakout Session

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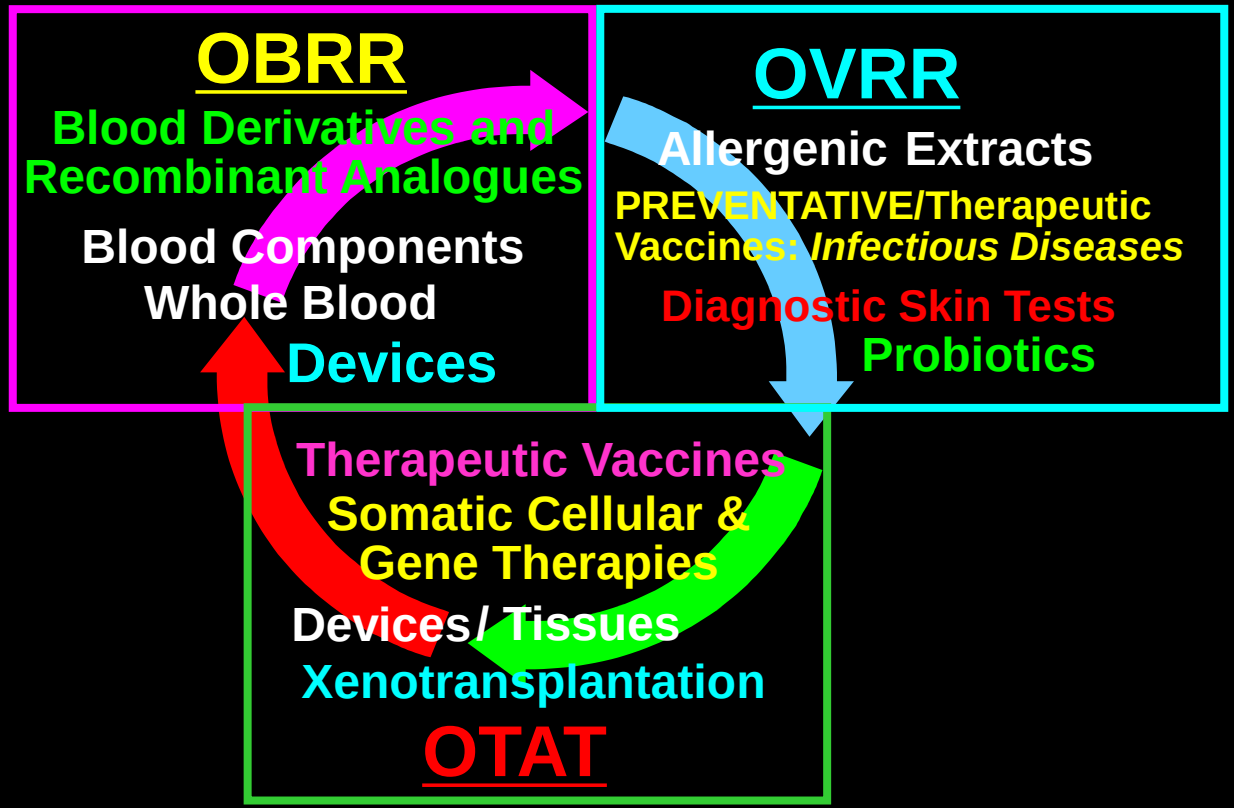
Office of Tissue and Advanced Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration

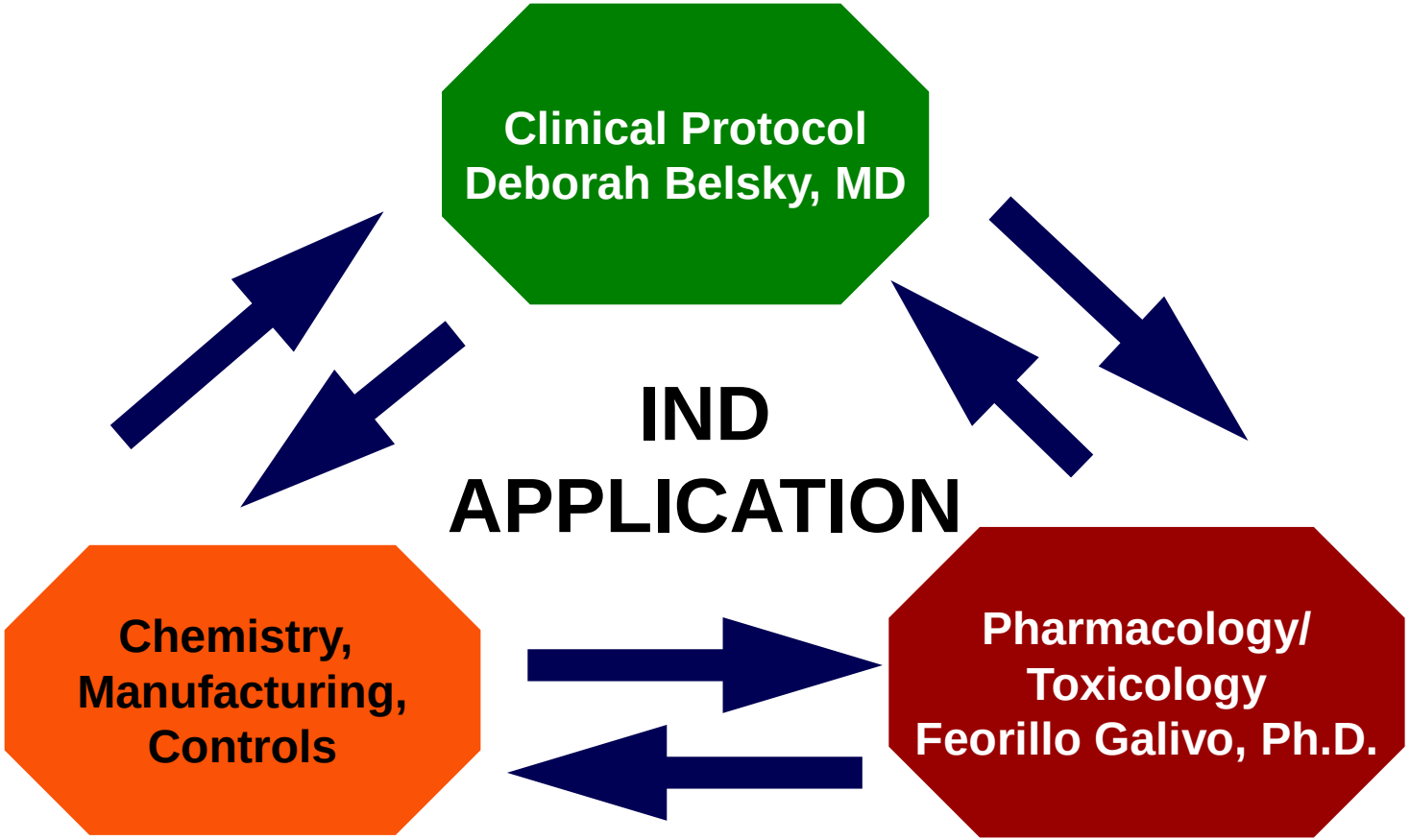
Learning Objectives

- Describe the team approach for IND original submission review and the interrelatedness between review disciplines.
- Objective of information supplied in the CMC section of the IND submission.
- Become familiarized with what to include in the CMC section of the IND original submission.
- Key CGMP concepts that support an early phase IND submission.
- Pre-submission interaction with FDA.

Products Regulated by CBER



Key Elements of the IND Submission



21 CFR 312.20 Subpart B: IND Application

☐	Form FDA 1571	*21 CFR 312.23(a)(1)*
☐	Table of Contents	*21 CFR 312.23(a)(2)*
☐	Introductory statement and general investigational plan	*21 CFR 312.23(a)(3)*
☐	Investigator's brochure	*21 CFR 312.23(a)(5)*
☐	Protocols	*21 CFR 312.23(a)(6)*
☑	**Chemistry, manufacturing, and control data (including environmental assessment**	*21 CFR 312.23(a)(7)*
☐	Pharmacology and toxicology data	*21 CFR 312.23(a)(8)*
☐	Previous human experience	*21 CFR 312.23(a)(9)*
☐	Additional information	*21 CFR 312.23(a)(10)*
☐	Biosimilar User Fee Cover Sheet	*Form FDA 3792*
☐	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.

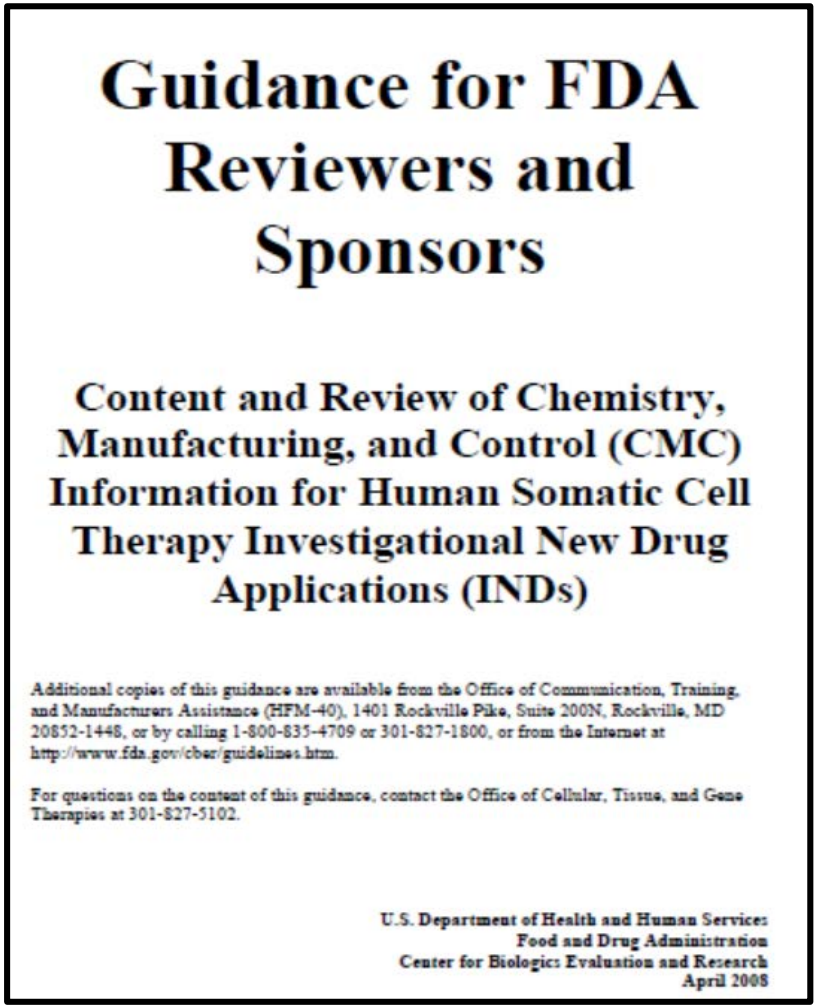
CMC ≈ *Can Manufacture Consistently*

Harnessing the Manufacturing Process

Chemistry, Manufacturing, Controls

Resource Guidance Document

https://www.fda.gov/media/73624/download



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 (INDs)

Additional copies of this guidance are available from the Office of Communication, Training, and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Office of Cellular, Tissue, and Gene Therapies at 301-827-5102.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
April 2008

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 may be the Same)

- 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 institution of an adequate system to identify product from the time of initial 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

Key CGMP Concepts

- CGMP regulations establish a minimum baseline for methods, approaches, facilities, and controls to be used for manufacturing, processing, packaging and/or holding of a drug/biologic to assure it is safe and meets identity, potency, quality and purity characteristics.

- **DOCUMENT, DOCUMENT, DOCUMENT:** ***If it is not documented, it did not happen / If it wasn't documented, it wasn't done***

- Adequate, accurate documentation is advantageous in the context of addressing deviations and investigating problems occurring during manufacturing.

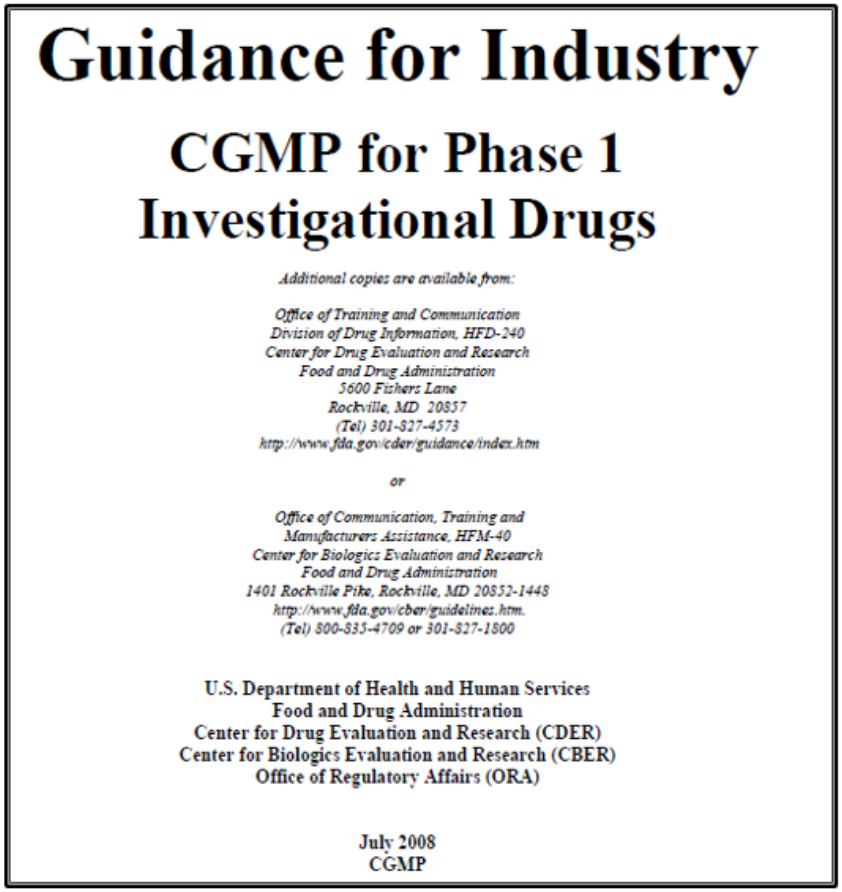
CGMP Requirement Flexibility

- CGMP requirements allow some flexibility permitting manufacturers to make determinations on how to implement certain manufacturing controls on a product-specific basis.
- Greater flexibility with respect to CGMP requirements is afforded during Phase 1, with expectations increasing as development proceeds toward late-phase studies (Phase 2/Phase 3).
- Manufacturing control determinations are made using scientifically sound design, processing methods and testing procedures.
- CGMP regulation flexibility allows innovators to use modern technologies and approaches in order to achieve a higher level of product quality through continual process improvement.
- “C” in CGMP represents “current”; expectation that platform technologies and systems used are up-to-date in order to comply with regulations.

Facts About the Current Good Manufacturing Practices (CGMPs):

https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps

CGMPs and Phase 1 Clinical Studies



Guidance for Industry

CGMP for Phase 1 Investigational Drugs

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) 800-835-4709 or 301-827-1800

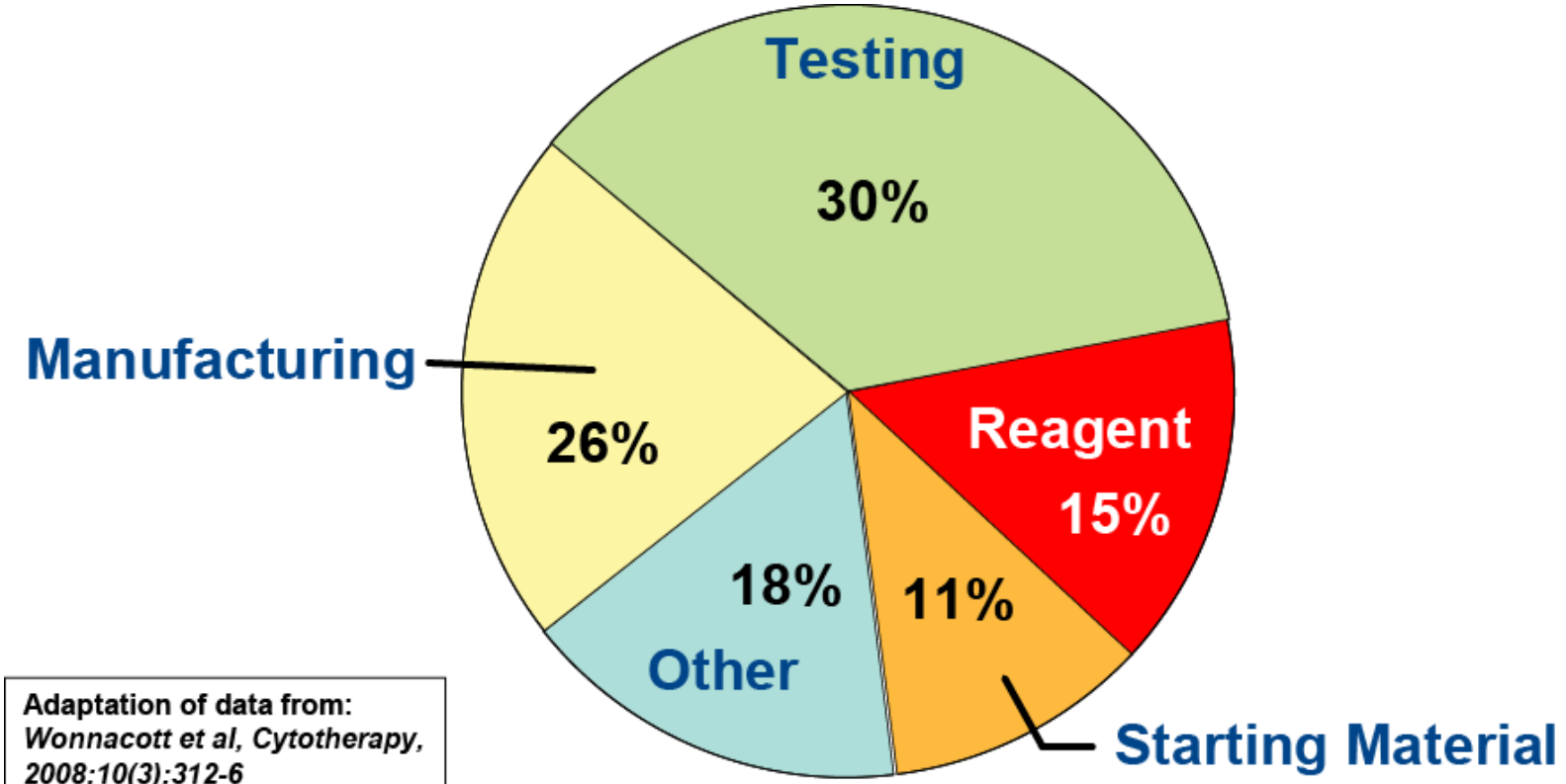
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

July 2008
CGMP

- Full compliance with CGMP regulations is **NOT** required for investigational products being evaluated in Phase 1 clinical studies.
  - Sponsor of IND application for Phase 1 clinical study is accountable for performing manufacturing and testing in accordance with information provided in CMC section of the IND.
  - The manufacture of investigational products under evaluation in Phase 2 and Phase 3 clinical studies is subject to full compliance of CGMP regulations in 21 CFR Part 211.
  - If an investigational product used in a Phase 1 clinical study has been lawfully marketed or made available in a Phase 2 of Phase 3 clinical study, must comply with 21 CFR 211.

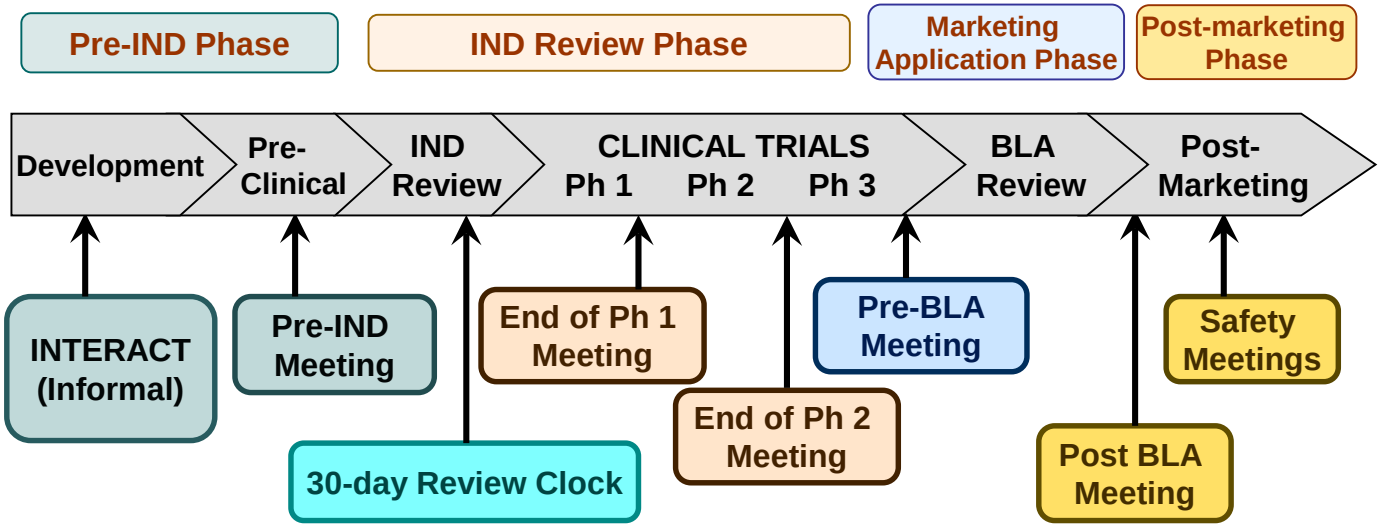
https://www.fda.gov/media/70975/download

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** (**In**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER Product**s**): Informal, Non-Binding Discussion: Generally CMC and Preclinical Topics, No Minutes Generated

  Website: https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings-initial-targeted-engagement-regulatory-advice-cber-products

- **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:*** 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

- CMC information included in an IND submission should demonstrate consistent, reproducible manufacturing capability.
- Sufficient CMC information should be provided to permit assessment of risk posed to subjects participating in a clinical study.
- CGMPs represent regulations that establish minimum manufacturing requirements to assure product safety and quality.
- Full CGMP compliance is not required for Phase 1 clinical investigation.
- For novel cell-based products pre-submission interaction with FDA is encouraged.

Challenge question

What is the objective intent of the information supplied in the CMC Section of an IND Submission?

To provide demonstration of a well-controlled process that is capable of reliable, consistent, and reproducible manufacture of the investigational product.

Contact Information

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  OTAT Main Line: 240-402-8190
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  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

Putting Together Your IND Submission (CBER): Preclinical Considerations

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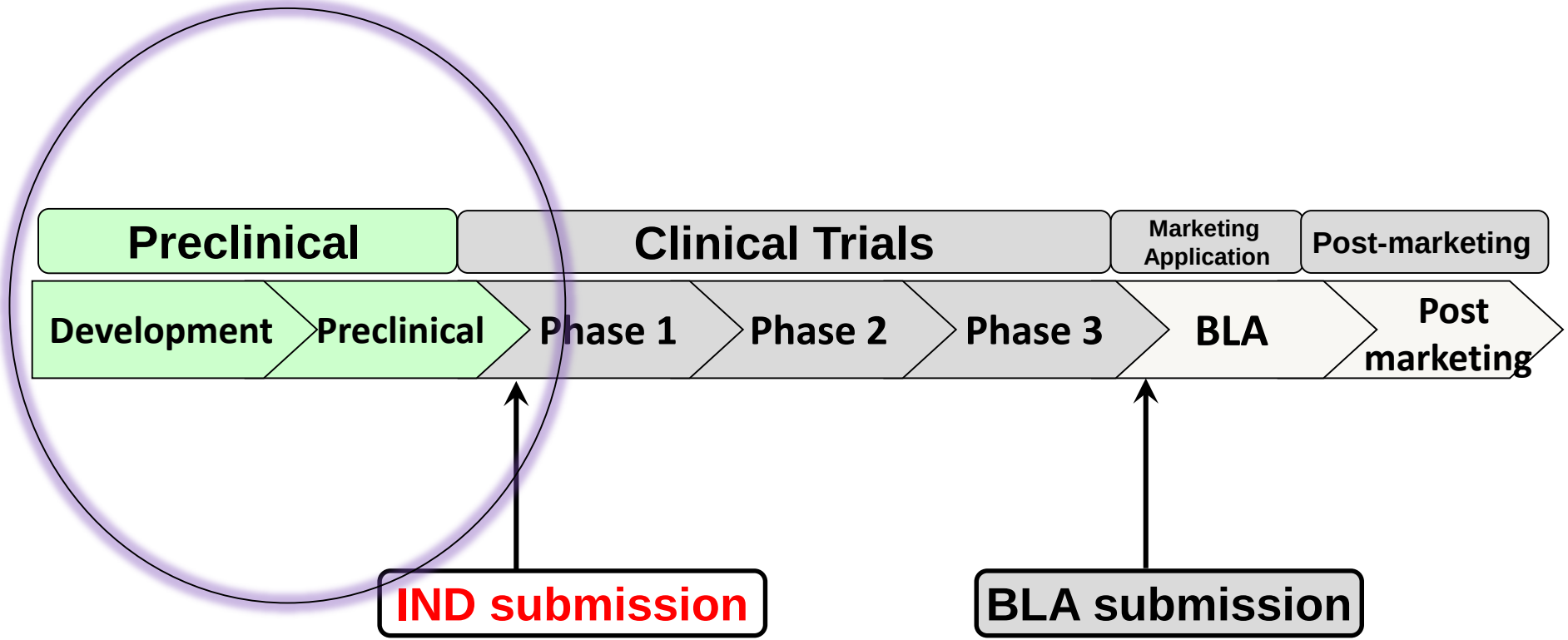
CLINICAL INVESTIGATOR TRAINING COURSE (CITC)
SESSION 5: INDs AND IDEs – A Cross-Center Perspective

Learning Objectives

- Gain familiarity with regulations governing preclinical testing
- Understand CBER review process
- Understand the preclinical expectations for early phase trials
- Decide when to have early interactions with the FDA
- Bookmark FDA Guidances and other online resources

Product Lifecycle for Biologics: Focus on the Preclinical Phase

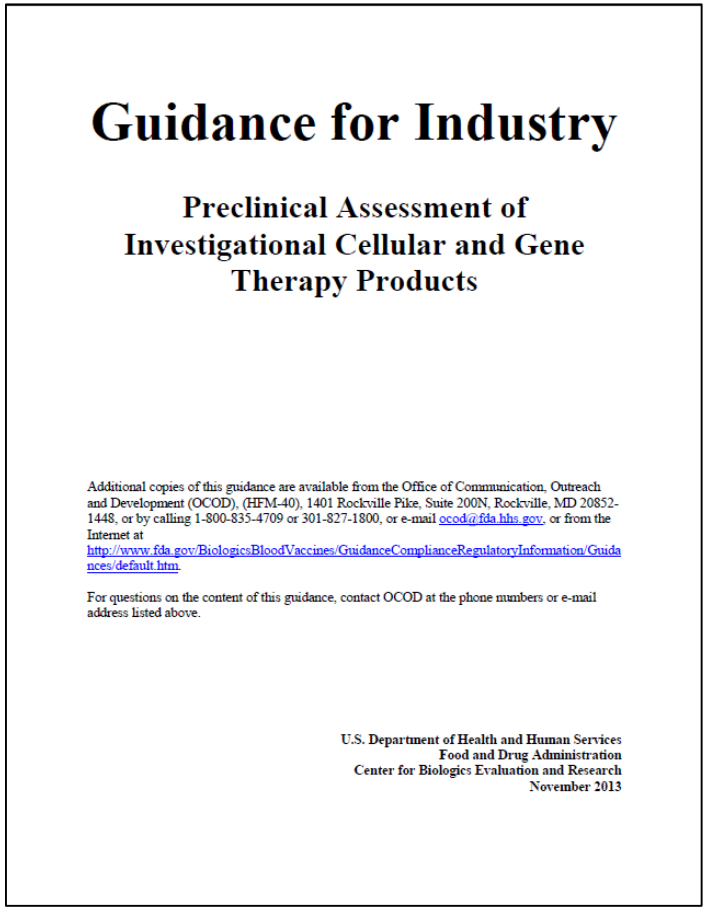


What Regulations Govern Preclinical Testing?

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

https://www.fda.gov/media/87564/download

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, 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 previous submissions to FDA
- Detailed clinical study reports from clinical trials

Preclinical Expectations for Early Phase Clinical Trials

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

Preclinical Expectations for Early Phase Clinical Trials

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

Preclinical Study Designs

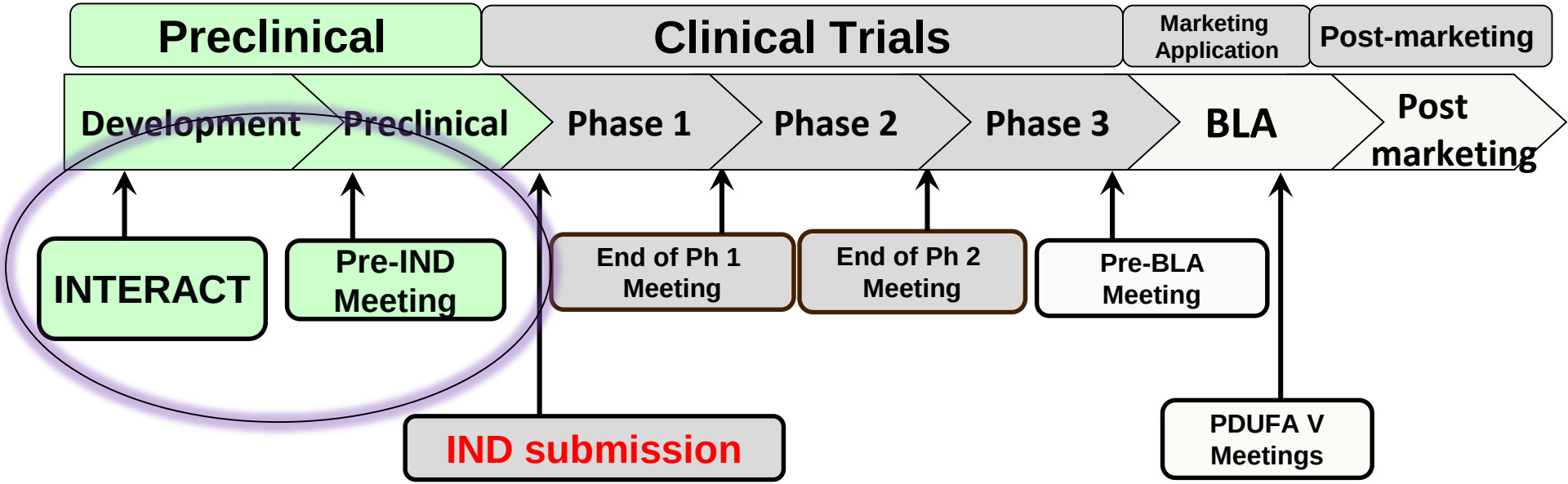
- Assess pharmacology / proof-of-concept (POC) / vector distribution / cell fate in relevant animal model(s) of disease / injury, as feasible
- Assess safety / toxicology (T) / vector distribution / cell fate in healthy animals
- Hybrid pharmacology-toxicology study design
  - POC + T + product fate – 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
  - both a rodent and a non-rodent species
  - 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*
  - *a specific investigational product or product-derivation strategy has been selected by time of INTERACT meeting request*

- **Goal:** *To obtain early feedback on a product development program for a novel investigational agent*

Early Communication with OTAT: *INTERACT*

- **Features:**
  - Non-binding, informal scientific discussions with CBER/OTAT review disciplines
  - Initial targeted discussion of specific issues (e.g., early product characterization, early POC studies, new delivery devices, general early-phase trial design elements)
  - FDA will help identify critical issues or deficiencies early in development

  - *Primary contact: INTERACT-CBER@fda.hhs.gov*

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

Pre-IND Meeting: Preclinical

- **What to include in the preclinical section?**
  - **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, 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 at the pre-IND meeting
- 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 and gene 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

Challenge question

What are the major objectives of a preclinical program for a CBER-regulated product?

- ✓Establish scientific rationale to support planned trial
- ✓Provide recommendations for the conduct of the proposed clinical study
- ✓To meet regulatory requirements

Selected Guidances

- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preclinical-assessment-investigational-cellular-and-gene-therapy-products

- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2017)

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-early-phase-clinical-trials-cellular-and-gene-therapy-products

- Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (July 2018)

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products

- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (October 2011)

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-considerations-therapeutic-cancer-vaccines

Contact Information

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  Email: OTATRPMS@fda.hhs.gov and

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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
- **Follow us on Twitter:** https://www.twitter.com/fdacber

I am John, a 56 year old geology professor with obstructive cardiomyopathy

My name is June. I am a 34 year old mother of three with a progressive, genetic, neurologic disease

All images in this presentation are copied from Google images

U.S. FOOD & DRUG ADMINISTRATION

Putting Together Your IND Application (CBER)

Clinical Trial Design Expectations to Ensure Safety for a First-in-Human Clinical Investigation

CDR Deborah S. Belsky, MD MPH, USPHS

Clinical Investigator Training Course

November 12-14, 2019

Objectives

Safety considerations in clinical trial design:

Understand how

- Subject selection criteria
- Investigational product characteristics
- Clinical protocol design

impacts subject safety

Design Expectations to Ensure Safety for a First-in-Human (FIH) Trial

Who

What

When

Place yourself in the shoes of the subject

Do the inclusion and exclusion criteria ensure the right subjects are selected to achieve the stated objectives and with the appropriate benefit risk relationship?

Cell and Gene Therapies: Choice of Study Population

FDA looks at overall benefit-risk for the study population

Safety Considerations:

- 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
  - Only one opportunity for subject- may not be able to participate in other clinical trials – (gene therapy)
  - Potential long-term complications or unknown and unexpected adverse events
  - Changes in immune function
  - Viral shedding is at least a theoretical risk? Could affect others

Choice of Study Population

Example: Patients with advanced disease and limited options

- Might be preferred population, if risks are acceptable in spite of uncertain benefit
- Might be more vulnerable to adverse events resulting from the investigational treatment
- Confounding adverse events due to underlying disease could make data difficult to interpret
- Advanced disease state may present irreversible pathology, which may not respond to the experimental therapy

FIH Trial – *WHO* will be included?

Criteria:

- Inclusion
- Exclusion
- Considerations with safety in mind:
  - age
  - co-morbid conditions
  - disease state
  - use of grading scales or other representations of disease status
  - concomitant meds

What

What are the characteristics of the investigational product and potential risks?

WHAT ARE THE POTENTIAL HARMS RELATED TO THE PRODUCT AND ITS ADMINISTRATION?

FIH Trial- Investigational product

WHAT

Type of Product

- Gene therapy
- Cellular therapy

Dosing plan

- Dose
- Dose escalation

Delivery Method

- Intravenous
- Intramuscular
- Intradermal
- Intrathecal
- Invasive procedure

When

WHEN – to Proceed/Stop

Staggering of subjects

Stopping rules

- Serious adverse events (SAEs)
- Adverse events (AEs)
- How many/what type of AEs before protocol stops or dose reduction?
- Dose escalation
- Dose Limiting Toxicity
- Individual subject treatment discontinuation

Procedures for Safety Assessments

Include sufficient descriptions of safety monitoring in your protocol, irrespective of phase of development.

Cell and Gene Therapies: Safety Considerations

- Staggered administration:
  - Most FIH trial
  - 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 dose escalation of products expected to provide only modest benefit

Clinical Hold for Safety Concerns

Protocol does not ensure safety of human subjects:

> "Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury"

Reference: 21 CFR 312.42 (b)(i)

Additional reasons for Clinical HOLD under 21 CFR 312.42 (b)

(ii) The clinical investigator(s) is/are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;

(iii) The investigator brochure is misleading, erroneous, or materially incomplete;

(iv) The IND does not contain sufficient information required under 21 CFR 312.23 to assess the risks to subjects of the proposed studies

(v) The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (*i.e.*, affecting reproductive organs) or developmental toxicity (*i.e.*, affecting potential offspring).

Safety and FIH Trials
Summary

- Consider *Who, What, and When*
- With thoughtful design, risks are minimized and objectives are achieved
- Most importantly, subjects are protected from unreasonable risks.

Challenge Question

1. In first in human trials, who should be enrolled?
    a. Healthy adult volunteers
    b. Patients with advanced disease
    c. Patients with mild disease
    d. Pediatric patients less than 2 years of age
    e. Any of the above depending on the clinical trial

Challenge Question

1. In first in human trials, who should be enrolled?
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Challenge Question

2. All of the following considerations are important for developing stopping rules except:

a. To inform the investigator when to stop a trial

b. To identify safety signals that might inform risk to subjects

c. To make subjects aware of when not to follow-up with the investigator

d. To place parameters around dose escalation trials to ensure safety to subjects

Challenge Question

2. All of the following considerations are important for developing stopping rules except:

a. To inform the investigator when to stop a trial

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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

Draft Gene Therapy Guidance documents in 2018:

- Treatment of Hemophilia
- Treatment of Retinal Disorders
- Treatment of Rare Diseases
- Long Term Follow-Up After Administration of Human Gene Therapy Products
- Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up
- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Questions?

U.S. FOOD & DRUG ADMINISTRATION

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- **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
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