FDA Framework for Gene Therapy Development

Kim Schultz, PhD
US Food and Drug Administration
Division of Cellular and Gene Therapies
CBER/OTAT

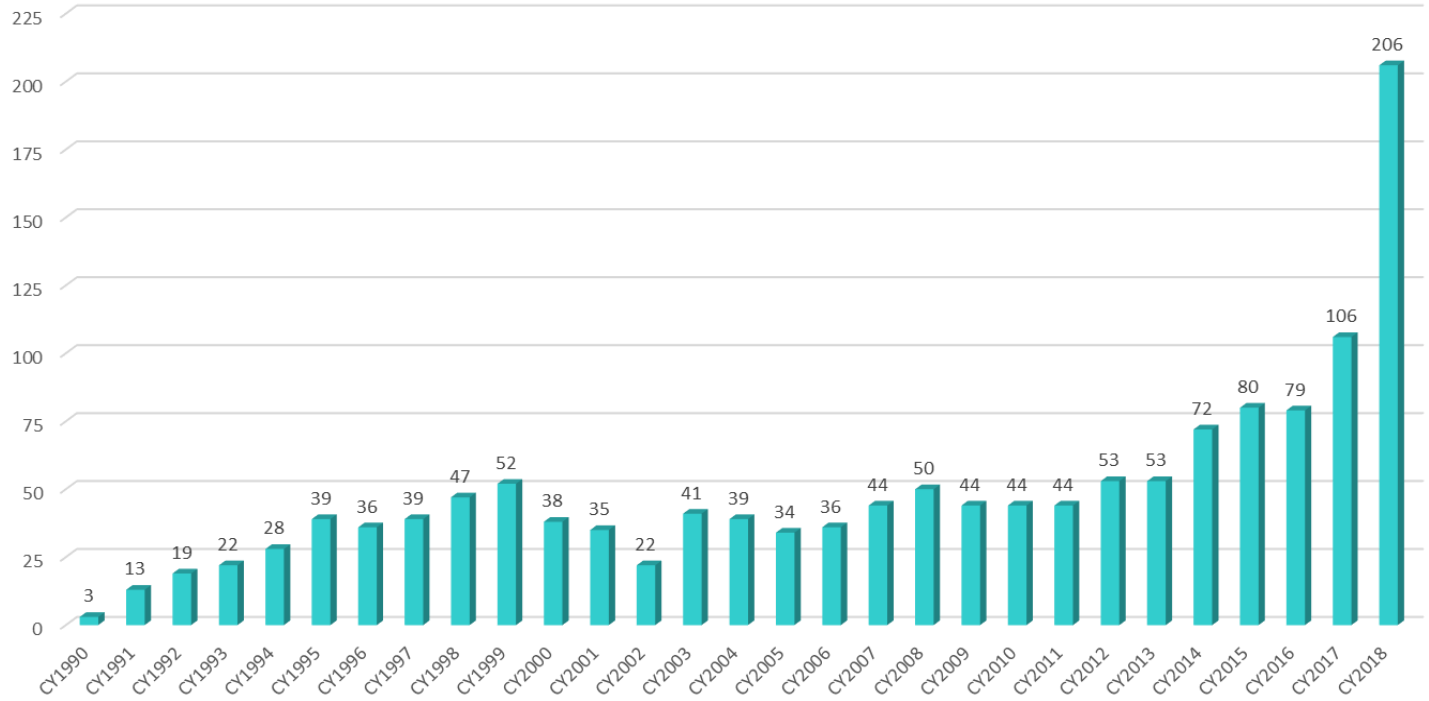
Human Gene Therapy (GT) Products

"mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host genetic sequences"

- Variety of products
  - Viral vectors
  - Bacterial vectors
  - Plasmid DNA, mRNA
  - Human genome editing products (e.g., gRNA, RNP, endonucleases)
  - Ex vivo genetically modified cells

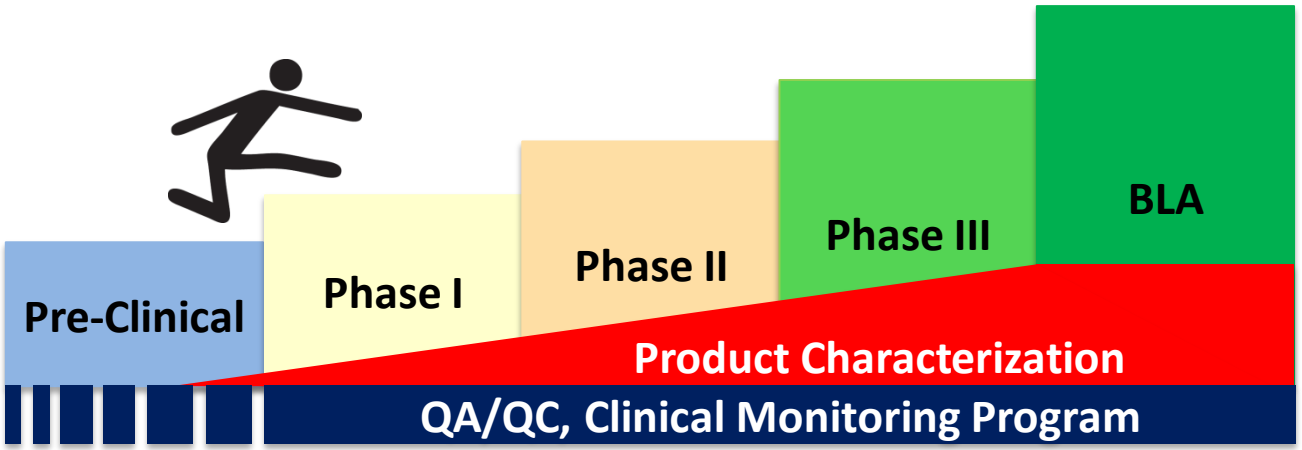
GT Field is Growing Rapidly

New Human GT IND Submissions (1990-2018)



Objective of FDA Review (21 CFR 312.22)

- Lifecycle approach to product development
- … in all phases of the investigation to assure the safety and rights of subjects
- ….and in phase 2 and 3 studies, to help assure that the quality of the scientific evaluation of drug product is adequate to permit an evaluation of the drug's effectiveness and safety



Recent CBER Guidance Documents:

- **Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)**: Draft Guidance for Industry (July 2018)
- **Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus during Product Manufacture and Patient Follow-up**: Draft Guidance for Industry (July 2018)
- **Observing Subjects Who Received Human Gene Therapy Products for Delayed Adverse Events**: Draft Guidance for Industry (July 2018)
- **Expedited Programs for Regenerative Medicine Therapies for Serious Conditions**: Guidance for Industry (February 2019):
- **Disease-Specific Guidances:** Draft Guidance for Industry (July 2018)
  - Human Gene Therapy for Hemophilia
  - Human Gene Therapy for Retinal Disorders
  - Human Gene Therapy for Rare Diseases

https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/ucm223006.htm

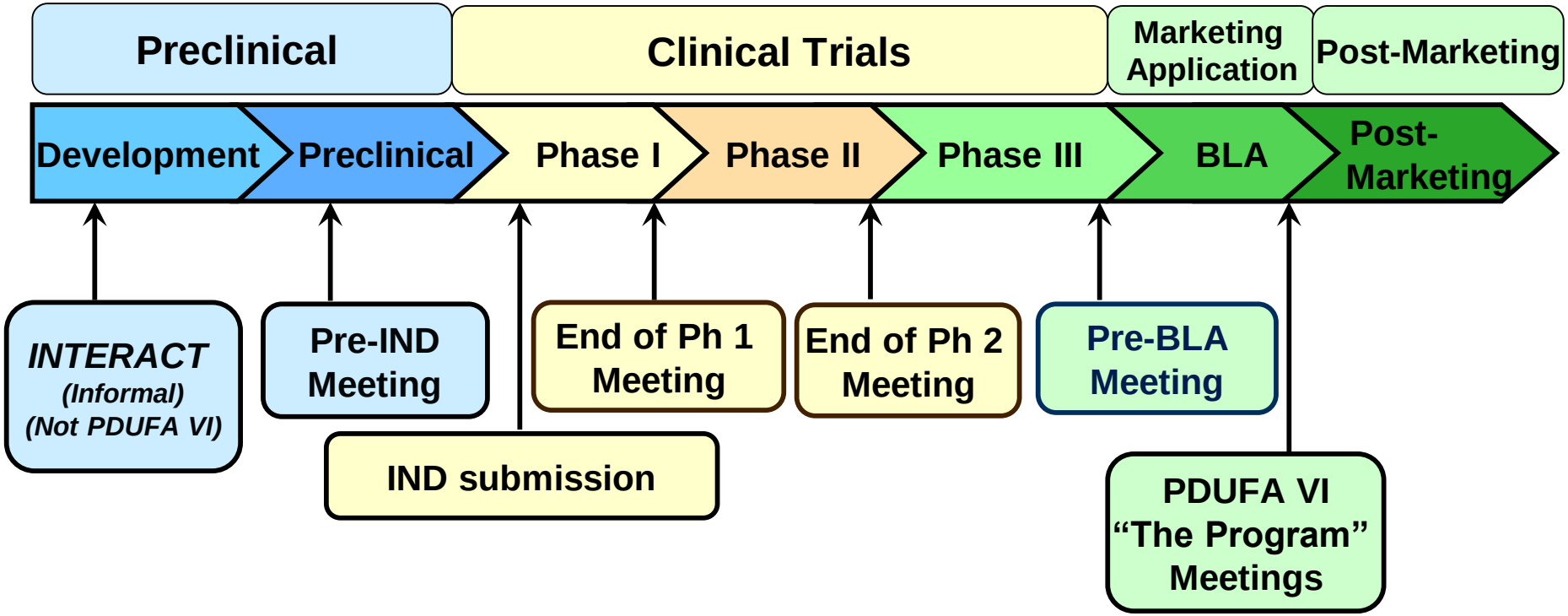
GT CMC Guidance

- Applicable to all GT products
  - Product class recommendations noted when applicable
- Organized into CTD format
  - Drug Substance (DS) section for vector used in manufacturing of ex vivo modified cells
- Regulatory requirements are phase specific
  - Phase 1 CGMPs
  - Product characterization and release criteria
  - Assay development, qualification, and validation

Navigating the FDA Framework During Global Development

- Align regulatory and scientific development through productive interactions
- Leverage accumulated data

Early Interactions Support Product Development



Designing a Global Development Regulatory Program

Preclinical:

- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products, 2013
- IPRP Reflection Paper on Biodistribution, 2018

CMC:

- Phase-specific, align with clinical development
- Comparability between products used for early and late phase studies

Clinical:

- Historical vs. active control
- Other available therapies
- Previous treatments
- Disease-specific guidances

Facilitating Development of Promising Therapies

Program	Intended function	Required information	Benefit
Breakthrough Designation (BTD)	To treat a serious or life-threatening disease or condition	Preliminary clinical evidence Demonstrate substantial improvement over existing therapies on ≥1 clinically significant endpoints	Intensive guidance on efficient drug development FDA Senior Management
Regenerative Medicine Advance Therapy (RMAT)	To treat, modify, reverse, or cure a serious or life-threatening disease or condition	Preliminary clinical evidence Potential to address unmet medical needs for such disease or condition	All features of BTD including early interactions to discuss potential Potential ways to support accelerated approval

Special Considerations for GT Products

- Small lot size, patient-specific lots or not many clinical lots
- Clinical programs may advance rapidly and the timelines from early to late development may be compressed
- Regulatory requirements do not change
- Planning for commercial manufacturing should be conducted early (Phase 1/2)
  - Product characterization and stability
  - Understanding effects of manufacturing changes
  - Choice of potency assay and relationship to clinical outcome for licensure

GT Assay Development

For INDs, **sufficient information is required at each phase of an investigation to ensure proper identity, quality, purity, strength, and/or potency**. The amount of information on analytical procedures and methods suitability will vary with the phase of the investigation.

- Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics (2015)

Early Phase Studies:

- Qualify assays used for product release and stability testing (suitable for the intended purpose)
- Develop characterization assays
- Explore a variety of product characteristics

Late Phase Studies:

- Validate critical assays (potency and dose)
- Lot release assays:
  Validation planned or completed
- Characterization assays:
  Developed & qualified
- Reference standards & controls:
  Developed & qualified

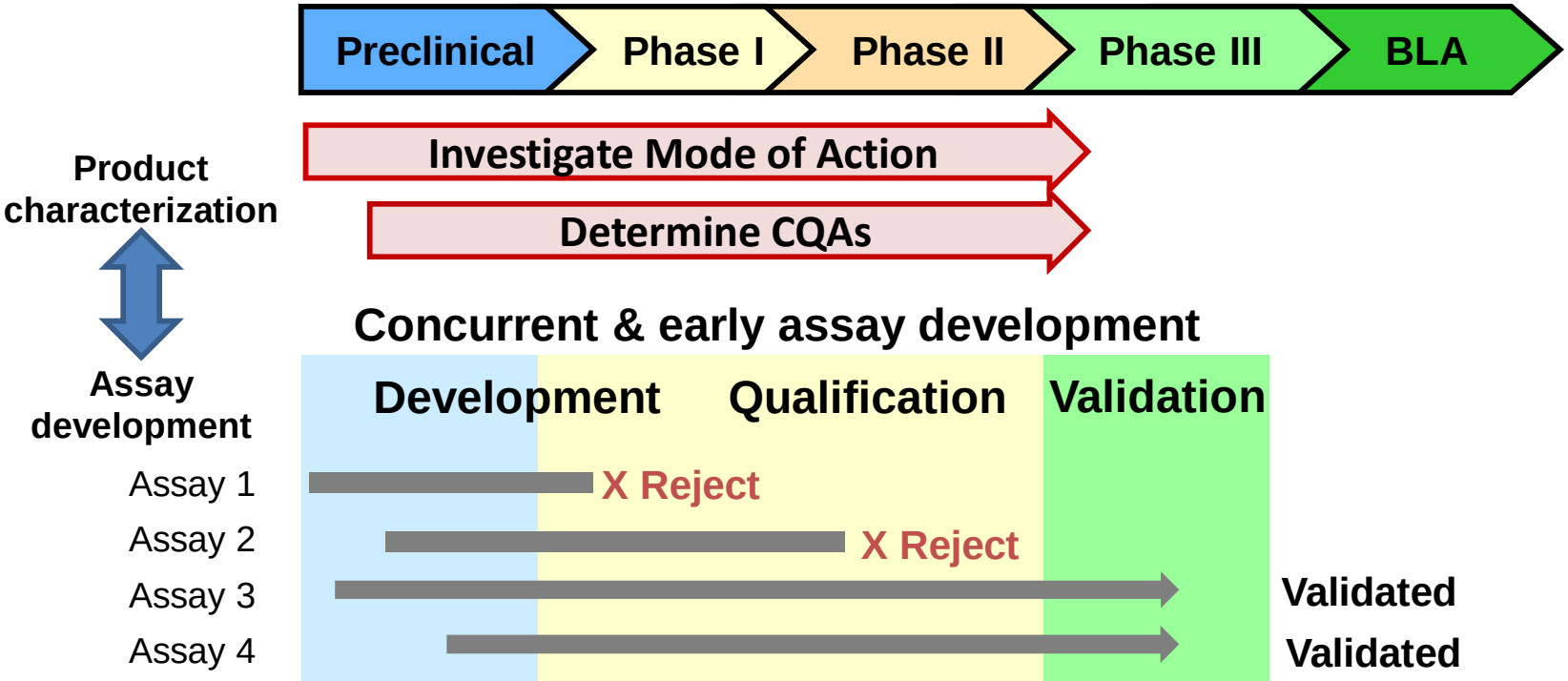
Encourage Early Product Characterization

A Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. *- ICH Q8 (R2)*

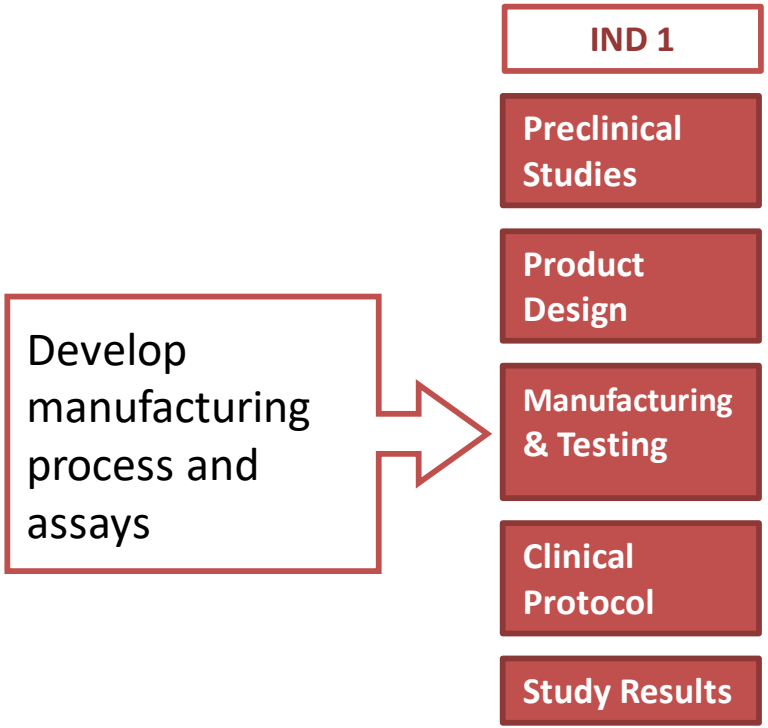
- Explore many CQAs during early development
  - Report results early in development
  - Choose relevant tests for late phase studies
- Evaluate multiple measures of CQAs, especially potency
  - Matrix of assays
  - Orthogonal methods
  - Stability indicating
- Support comparability studies

Concurrent & Early Assay Development

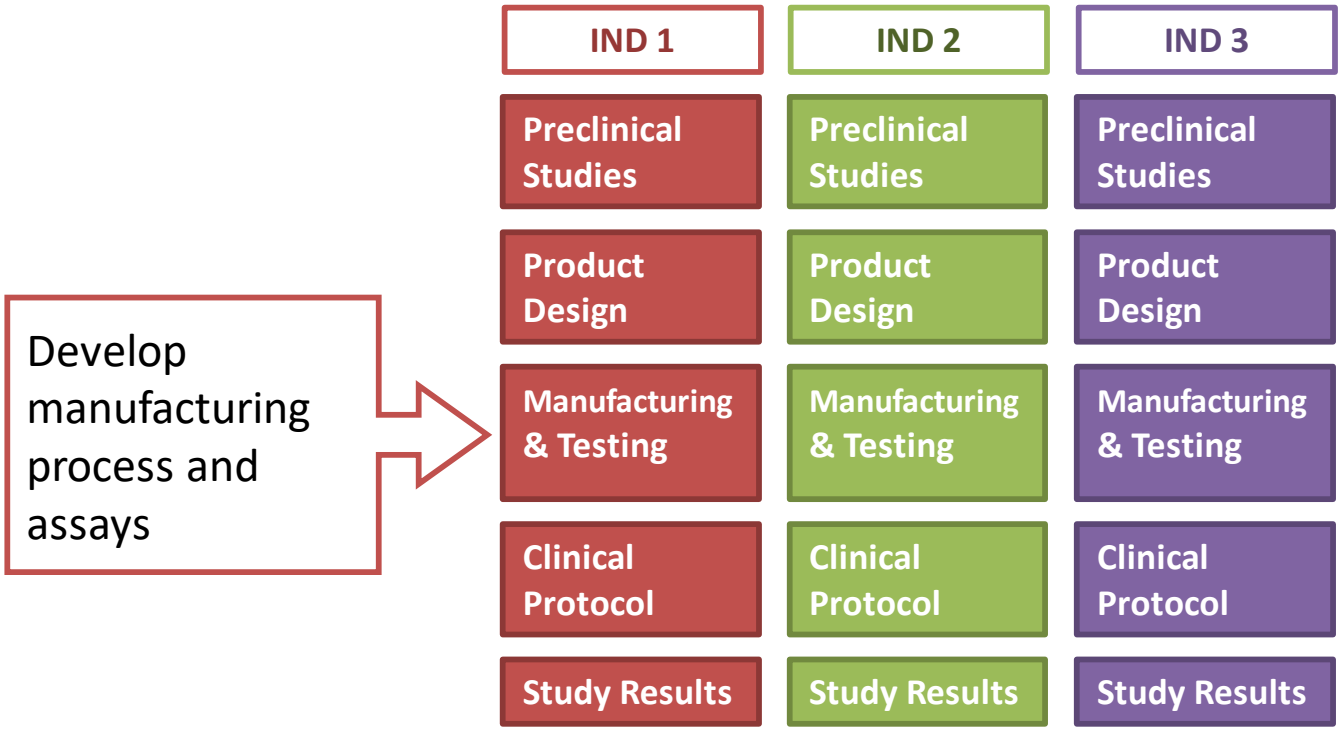
Early product characterization can support assay development for key product attributes (potency, purity, identity)



Leverage Development Across Similar Products

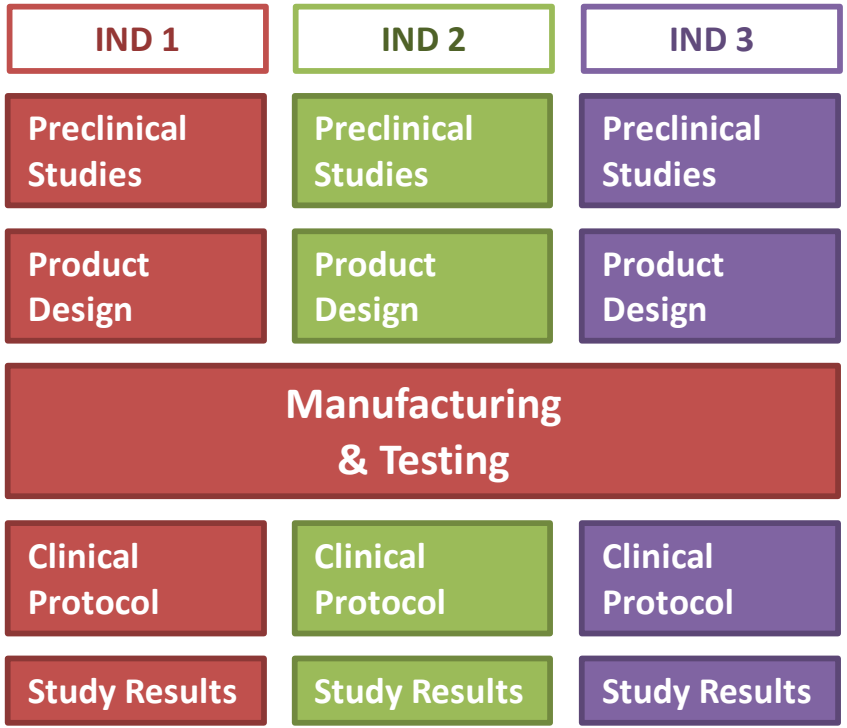


Leverage Development Across Similar Products



Leverage Development Across Similar Products

- Example: cross-referencing manufacturing information
- Clearly state the information you are referencing and where it is located in the file
- Referenced information does not need to be repeated; only include information specific to your product
- Submit a letter of authorization to cross reference an IND if you are not the Sponsor; referenced information remains proprietary



CBER Drug Master Files (MF)

- MF holder authorizes sponsors to rely on the MF information to support a submission to FDA without the having to disclose the MF information
- Submit directly to CBER for GT-related MFs
- DRAFT Drug Master Files Guidance for Industry (October 2019)

Common CBER MF Type	Information	Examples
2	Manufacturing process	CMO manufacturing Manufacturing and testing of a DS (e.g., vector) or reagent
5	Reference material	CMO facility description QA/QC information

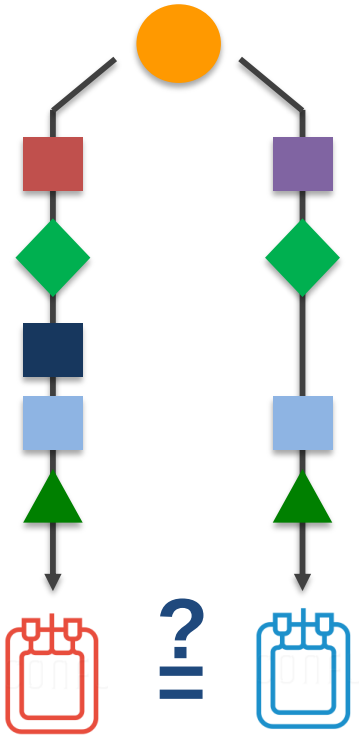
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-master-files-guidance-industry

CMC Changes During Development

- Manufacturing process change
- Manufacturing facility change
- Additional manufacturing facilities

Analytical Comparability Study Considerations

- Recommend making changes prior to initiating clinical studies intended to support efficacy for licensure
  - If changes are introduced in late stages of development with no additional clinical studies planned to support the BLA, the expected level of comparability demonstration will be significantly higher.
  - If analytical comparability study data are not sufficient to establish comparability, additional pre-clinical and/or clinical studies may be required to demonstrate comparability of product safety and efficacy.
- Establishing comparability allows combined analysis of efficacy data
- Comparability protocol should be developed and discussed with FDA prior to performing the comparability assessment



Challenges for Establishing Comparability

- Limited manufacturing experience:
  - Not many lots produced
  - Not enough retention or test samples available
- Limited in-process testing: process variables and CPPs not known
- Limited product characterization: CQAs not known, product and process related impurities not well characterized
- Limited assay development (e.g., purity, potency)
  - Assays not qualified or not stability indicating
  - Reference standards not established or adequately characterized

Summary

GT products are complex in composition and how they are manufactured.

We recommend that sponsors:

- Align scientific and regulatory development with clinical study timeline.
- Identify the critical quality attributes of the product early in development.
- Develop a matrix approach for measuring certain CQAs of the product (in cases where it is feasible).
- Build a robust analytical tool box not only for product release testing but also for product characterization, stability testing, and in-process testing.

Contact Information

- **Kimberly Schultz, PhD**
  kimberly.schultz@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
- **Follow us on Twitter:** https://www.twitter.com/fdacber


FDA
U.S. FOOD & DRUG
ADMINISTRATION