CBER's CMC Considerations for Early Phase Studies of Cell and Gene Therapy Products

Karin Knudson, Ph.D.
CMC Reviewer,
Office of Cellular Therapy and Human Tissue CMC,
Office of Therapeutic Products
CBER | US FDA

Regulatory Do's and Don'ts: Tips from FDA Staff
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Learning Objectives

- Understand why manufacturing investigational cell and gene therapy (CGT) products presents unique challenges.
- Identify the Chemistry, Manufacturing, and Control (CMC) information to include in your early phase investigational new drug (IND) submission.
- Describe common CMC issues during the product development lifecycle and approaches for avoiding them.

Diversity of Products Regulated by Office of Therapeutic Products (OTP)*

Gene Therapy Products (GTPs)

- Ex vivo modified genetically engineered cells: stem cells, immune cells (e.g., CAR-T, NKT)
- Genome-edited T cells or stem cells
- Microbial vectors (e.g., Listeria)
- Viral vectors (e.g., AAV, AdV)
- Oncolytic viruses
- Tumor vaccines: peptides (tumor derived or synthetic)
- Plasmids, mRNA

Cell Therapy Products (CTPs)

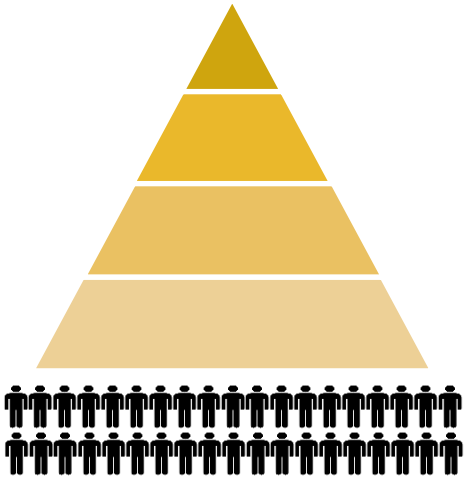
- Stem cells (e.g., HSCs, MSCs, cord blood-derived cells)
- Cell products derived from pluripotent stem cells (e.g., iPSCs, ESCs)
- Pancreatic Islets
- Anti-tumor and anti-viral T cells
- Innate immune cells
- Chondrocytes
- Hepatocytes
- Xenotransplantation products

* This is not an all-inclusive list

Different Manufacturing Paradigms

Conventional Drug/ Biologic

1 product lot



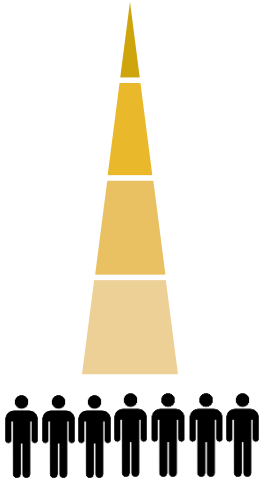
Many patients

Unique issues for CGT products

- Advanced manufacturing
- Advanced QC technologies
- Scale up/scale out
- Comparability
- Source materials
- Distribution
- Impact of manufacturing failure

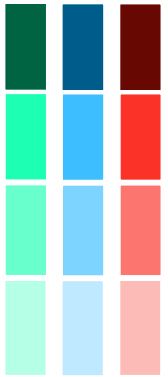
Cell & Gene Therapy (CGT) Products

1 product lot



Few patients

1 product lot



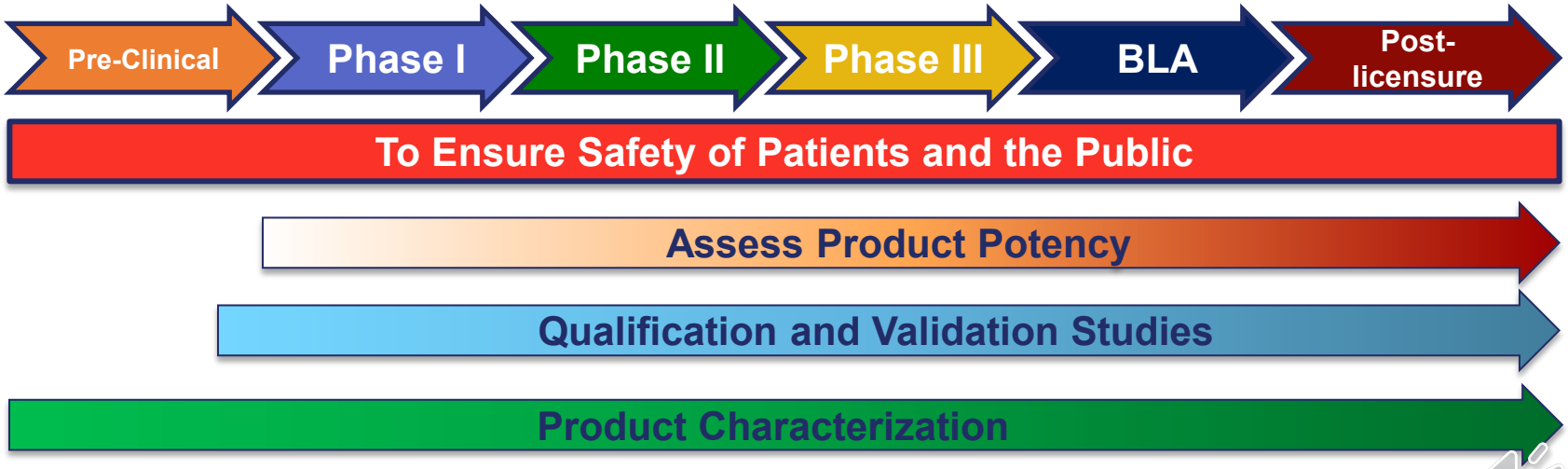
Single patient

Regulatory review of cell and gene therapy products is highly product dependent

- Scale: one “lot” could treat thousands of patients or just one
- Manufacturing procedures, technologies, and methods differ widely
- Comprehensive testing is challenging for products with little test material or very short shelf lives
- Risk of product depends on source material and how the product is made
- High inherent variability of some product types makes demonstrating manufacturing comparability and consistency challenging

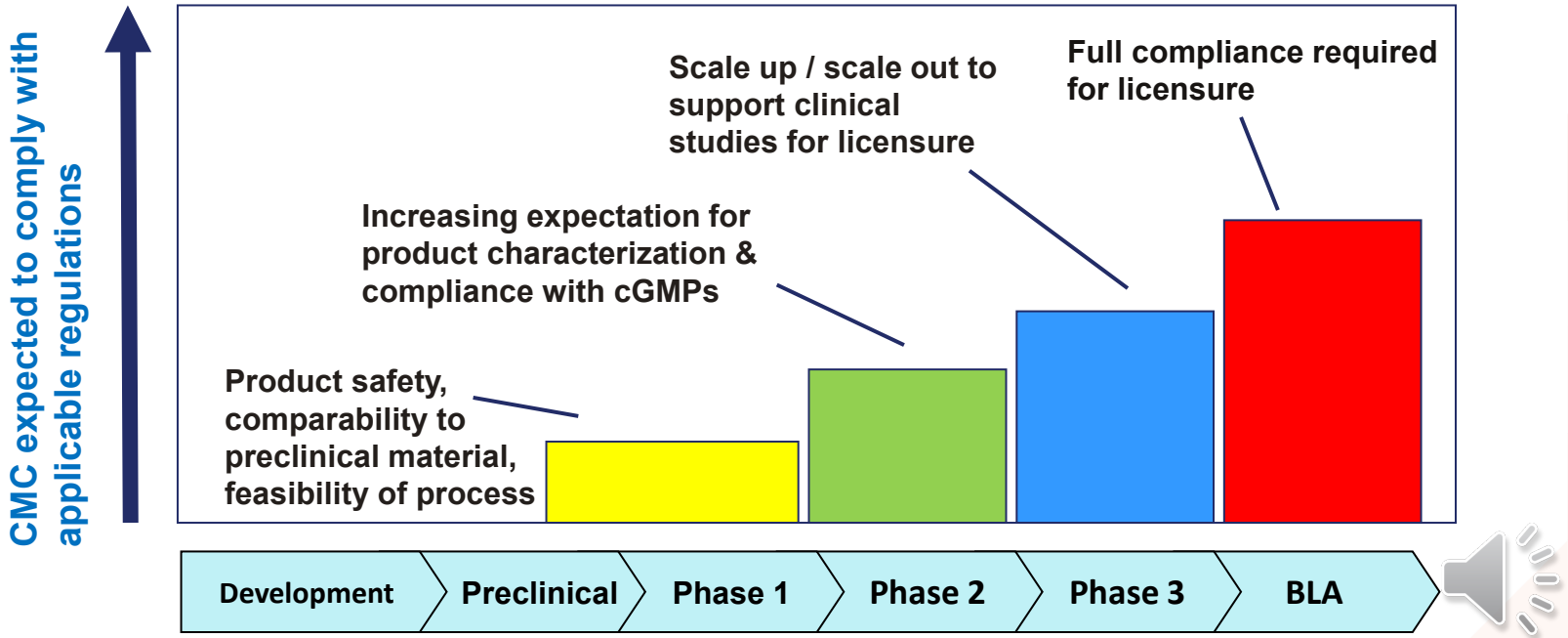
Product Development Lifecycle

- The stage of product development guides the review concerns, with **safety** being the primary concern at all stages



- Safety and quality must be **designed into** the product
- Start early!

Cell and gene therapy product development should progress in parallel with clinical development



Chemistry, Manufacturing, and Controls (CMC)

- Safety of source materials, intermediates, and final product
  - Details of product manufacturing
  - Details of raw materials used for manufacturing
  - Manufacturing process and quality systems
  - Product safety and quality testing (in-process and release testing)
- Product stability, storage and shelf life
- Container, label, and tracking information
- Cross-reference related INDs or Master Files

CMC Information Provided in an Investigational New Drug (IND) Application

Demonstrate Capability to Consistently and Reproducibly Manufacture the Investigational Product

- Should include information that describes **composition**, **manufacture**, and **control** of the investigational product.
- Should be sufficient to assure **identity**, **quality**, **purity**, and **potency** (biological activity) of the investigational product.

21 CFR 312.23(a)(7)

CMC Information Provided in an Investigational New Drug (IND) Application

- Early phase is more focused on **safety**: identity, purity, and activity
- The amount of information to be submitted will depend on the phase and scope of the initial clinical investigation.
- As development proceeds, it will be necessary to supplement initial CMC information as appropriate to address the expanded phase and scope of clinical investigations.
- Later phases require more information on **quality and potency**

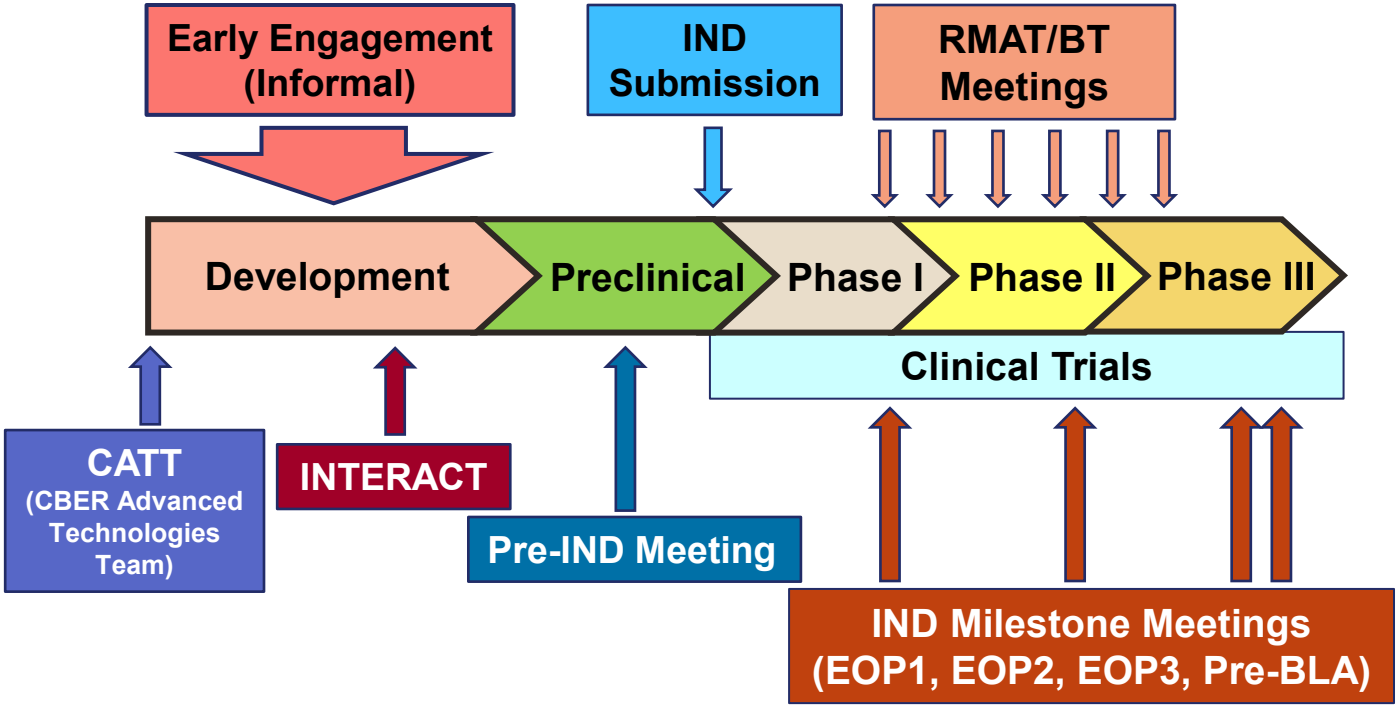
Common CMC Issues: Early Phase Studies

Some product safety issues to consider:

- Donor eligibility: autologous vs. allogeneic
- Release assays: methodology, controls/reference standards
- Sterility and mycoplasma assays: methodology, rapid assay, qualified?
- Dose measurement assay: different for preclinical studies than for clinical studies; qualified?
- Critical raw materials/reagents: source, documentation, COA
- Delivery device: regulatory status, investigational, compatible with drug product?

…not an all-inclusive list!

Early Phase Interaction With CBER/OTP



Summary

- The CMC information submitted under early phase INDs should demonstrate capability to consistently and reproducibly manufacture a **safe** investigational product.
- CMC regulatory review of cell and gene therapy products is highly product dependent.
- Talk to regulators about challenging issues or novel approaches.
- Safety and quality must be designed into the product, so **start early**!

Contact Information

Karin Knudson: Karin.Knudson@fda.hhs.gov

Regulatory Questions:

OTP Main Line: 240-402-8190
Email: OTPRPMS@fda.hhs.gov

Interactions with Office of Therapeutic Products website:
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OTP Learn Webinar Series: OTP Learn

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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