

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

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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



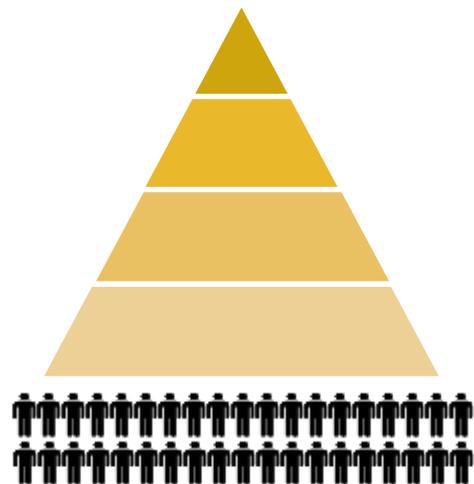
* This is not an all-inclusive list

Different Manufacturing Paradigms



Conventional Drug/ Biologic

1 product lot



Many patients

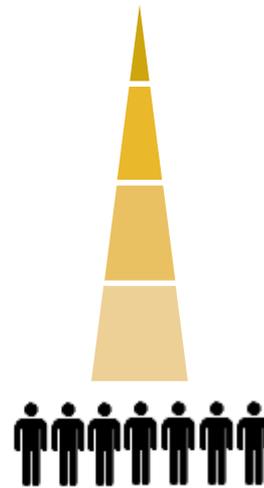
Unique issues for CGT products

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

Impact of manufacturing failure

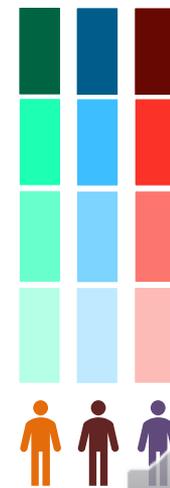
Cell & Gene Therapy (CGT) Products

1 product lot



Few patients

1 product lot



Single patient

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



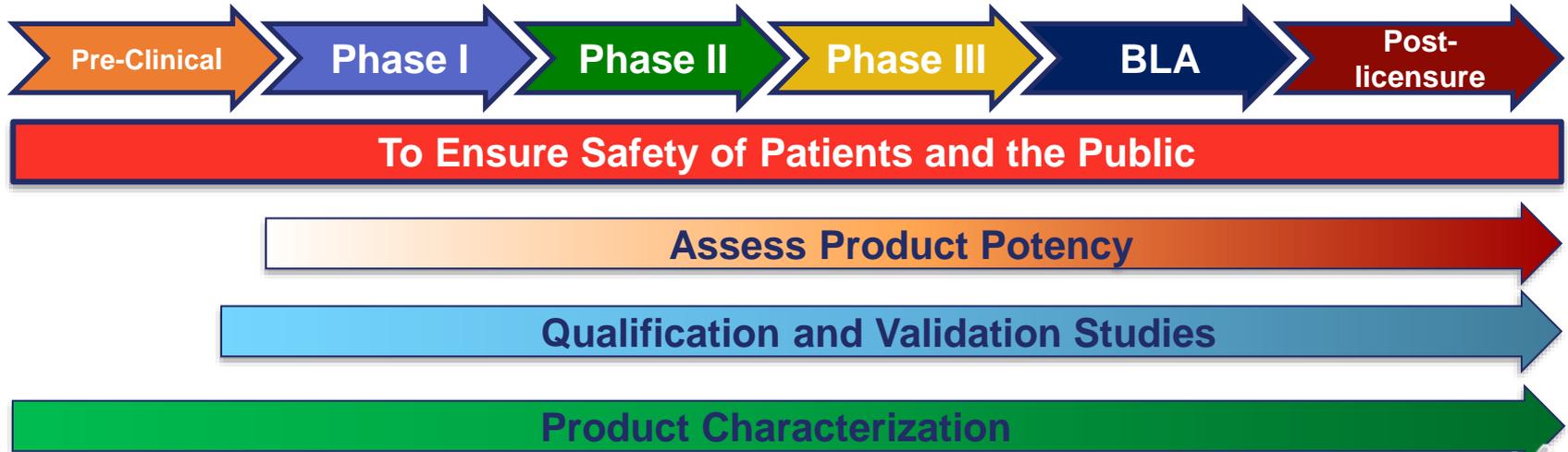
- Scale: one “lot” could treat thousands of patients or just one
- Manufacturing procedures, technologies, and methods differ widely
- Comprehensive testing is challenging for products with little test material or very short shelf lives
- Risk of product depends on source material and how the product 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



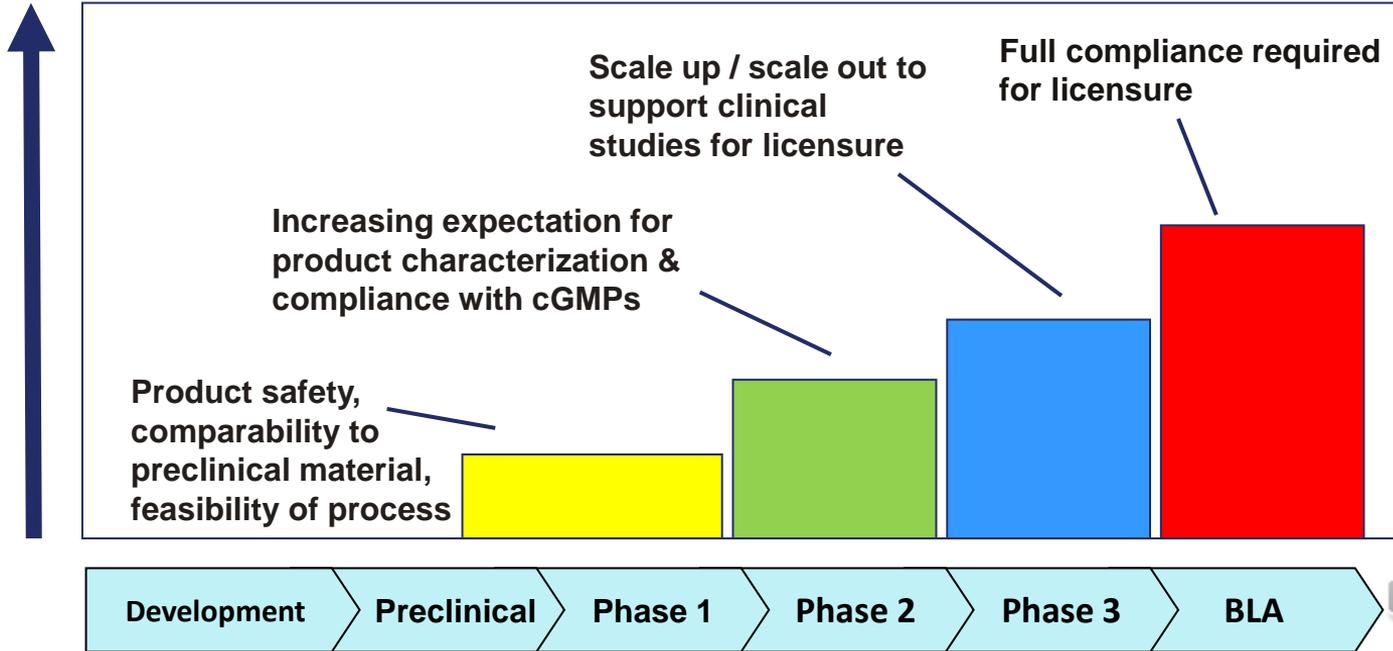
- Safety and quality must be **designed into** the product
- Start early!



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



CMC expected to comply with applicable regulations



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.



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



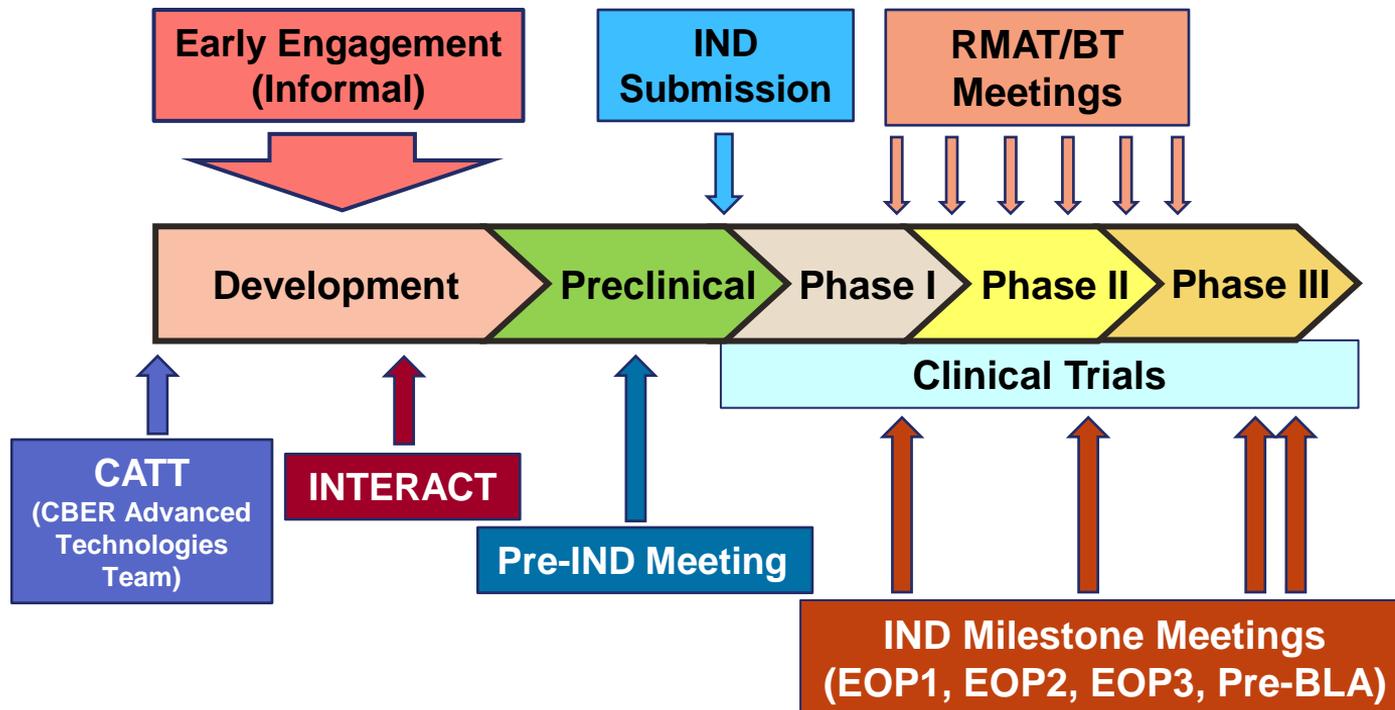
Some product safety issues to consider:

- 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!**



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