

# Common Product Quality Issues for Cellular and Gene Therapy Products

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# Learning objectives

- To recognize the types of products regulated by the Division of Cellular and Gene Therapies (DCGT), Office of Tissues and Advanced Therapies, CBER.
- To recognize challenges associated with the chemistry, manufacturing and control (CMC) for cell and gene therapy (CGT) products throughout product development.
- To understand the advantages and challenges associated with expedited product development programs.
- To be aware of key FDA guidance documents and other resources for the CMC issues in the development of CGT products.

# Diversity of products regulated by DCGT\*

## Gene Therapy Products (GTPs)

- Ex vivo modified genetically engineered cells: stem cells, immune cells (CARTs, 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: HSCs, MSCs, cord blood-derived etc.
- Cell products derived from pluripotent stem cells (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

# Regulatory decision making

- FDA's regulatory decisions in the pre-market and post-market review process are based on a benefit-risk assessment.
- Every regulatory decision involves a unique risk/benefit assessment for the disease, patient population, and agent(s) being evaluated.
- This assessment is informed by science, medicine, policy, regulations, relevant scientific literature and judgment.
  - **Data-driven decision making**

# Regulatory review at FDA is highly product dependent...

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

# Chemistry, Manufacturing and Controls (CMC)

- Safety of source materials, reagents, intermediates, and final product
  - Details of product manufacturing
  - Manufacturing process and quality systems
  - Product safety and quality testing
- Product stability, storage and shelf life
- Container, label, and tracking information
- Cross reference related Investigational New Drug (IND) Applications or Master Files

# Understand Current Good Manufacturing Practices (CGMP)



- GMP is more than just a “state of the art facility”
- FD&C Act at 501(a)(2)(B) statute requires biologics to be manufactured in accordance with current good manufacturing practices. FDA regulations for GMP are covered in 21 CFR 210/211.
- There is more than one way to be GMP compliant
- Facility design is dictated by the products being manufactured
- Many GMP facilities manufacture more than one product – need to properly segregate and track each product

# CMC information provided in an 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.
  - Early phase is more focused on safety: identity, purity, and activity
  - Later phases require more information on quality and potency
- 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.

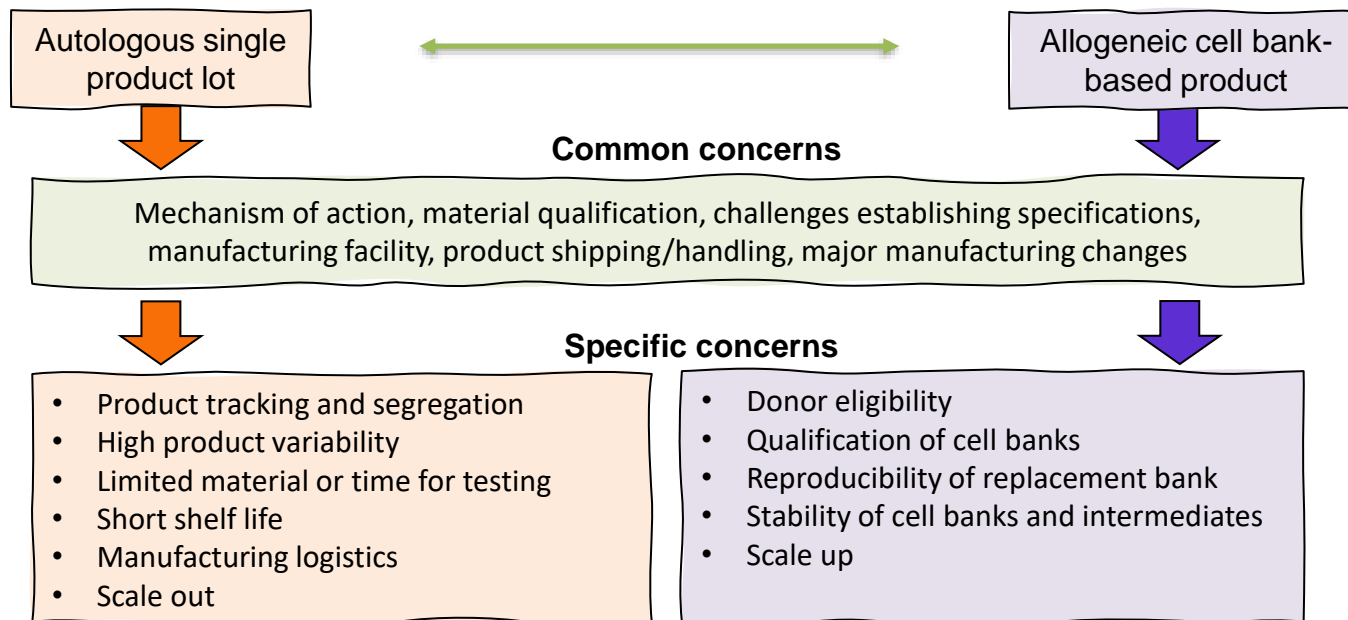


# CMC expectations for late-stage CGT development



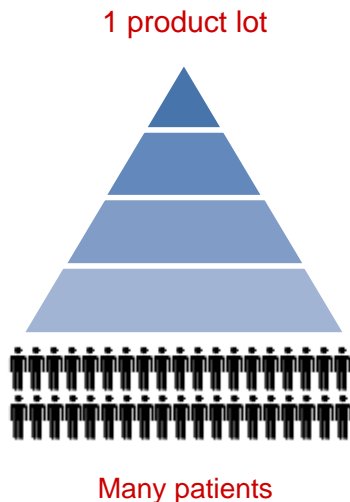
- Have a controlled manufacturing process
  - Sufficient knowledge of the manufacturing process to determine Critical Process Parameters (CPP)
  - Sufficient knowledge to set in-process quality criteria: Action Limits and Rejection Limits
  - Sufficient knowledge to plan for future production scale up/scale out
- Have well developed and qualified/validated analytical assays
  - Have a biologically relevant potency assay in place
- Have sufficient manufacturing experience to refine product acceptance criteria

# Unique CMC challenges for CGTs



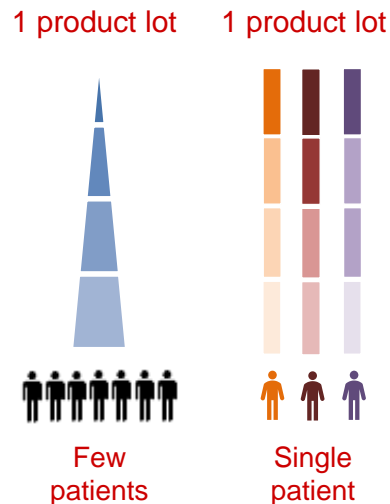
# Different manufacturing paradigm

## Conventional Drug/Biologic



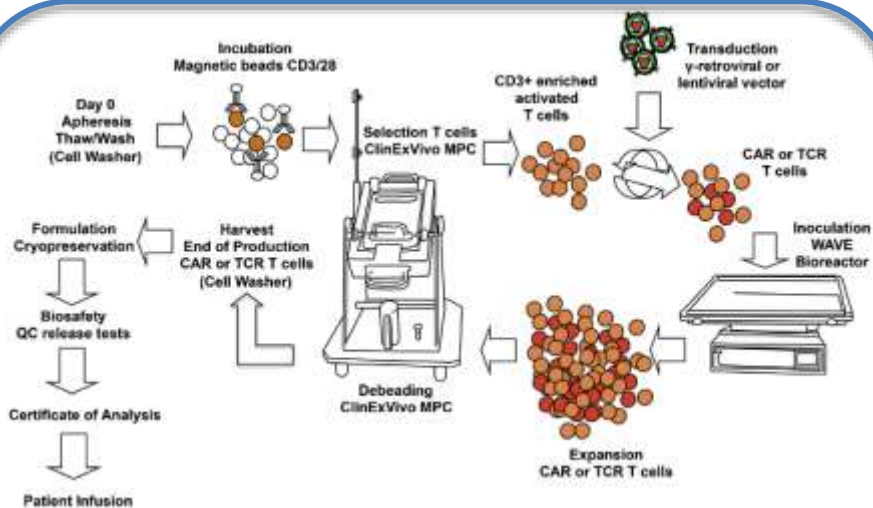
Raw materials  
CGMPs  
Advanced manufacturing  
In process and lot release testing  
Scale up/scale out  
Comparability  
Distribution  
Impact of manufacturing failure

## Cell & Gene Therapy (CGT) Products



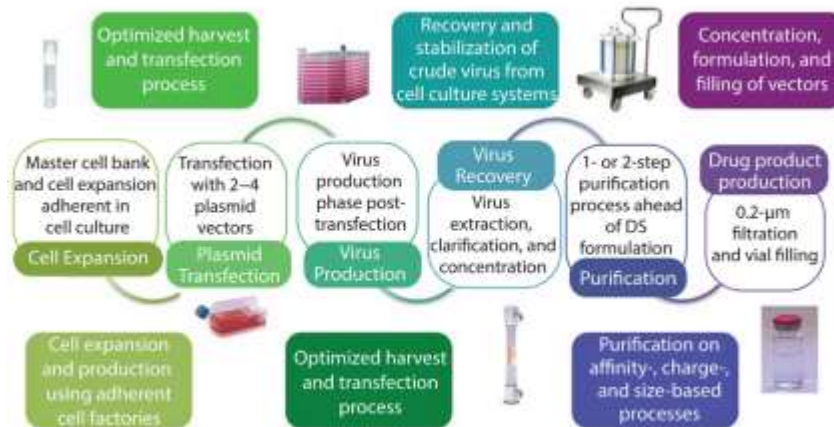
# CGT product manufacturing is complex

## Autologous engineered T cell manufacturing



Themeli et al., 2015

## AAV vector manufacturing



Hitchcock et al., 2017

- There is often a need for significant in-process characterization.

# Issues in the manufacture of gene therapy vectors

- Lack of capacity for manufacture of lentiviral and adeno-associated virus (AAV) vectors is limiting clinical development
  - Bottleneck for both academic research and commercial R&D
  - Building manufacturing capacity in the US is crucial
- Current manufacturing processes and facilities are not able to meet demand, despite some improvement over the past few years.
- Opportunities:
  - Cell selection producing the highest amount of vector
  - Growing cells in modern bioreactors vs. tissue culture flasks – increased cell density and reduces the need for manual processing
  - Optimize downstream purification scheme to reduce loss of vector, during chromatography and sterile filtration.

# Issues in the manufacture of cell therapies

- Process must be developed to consistently manufacture and characterize cells
  - Scale-out vs. scale-up
- Logistics of manufacturing for autologous cells can be challenging
  - Increased automation
- Potential and challenges of allogeneic cell therapies
  - Allogeneic cell line (one product, “universal” or “off-the-shelf”) may be preferred and scaled-up
  - Rejection by the immune system

# CGT product: unique manufacturing challenges



- Limited product manufacturing experience prior to licensure (incomplete knowledge of Critical Process Parameters (CPP), limited lots made)
- CQAs not entirely understood due to limited characterization of drug product, drug substance, and in-process material
- Product variability arising from source materials
- Increased demand for qualified reagents and materials
- Assays not fully developed and qualified
- Limited time for testing due to limited material or short shelf-life
- Limited product stability data
- Reproducibility of replacement cell banks
- Complicated planning for advanced manufacturing, process automation, scale up / scale out
- Comparability studies in the absence of reliable reference standards and validated assays
- Direct impact of manufacturing failure on patient



# Challenge question #1

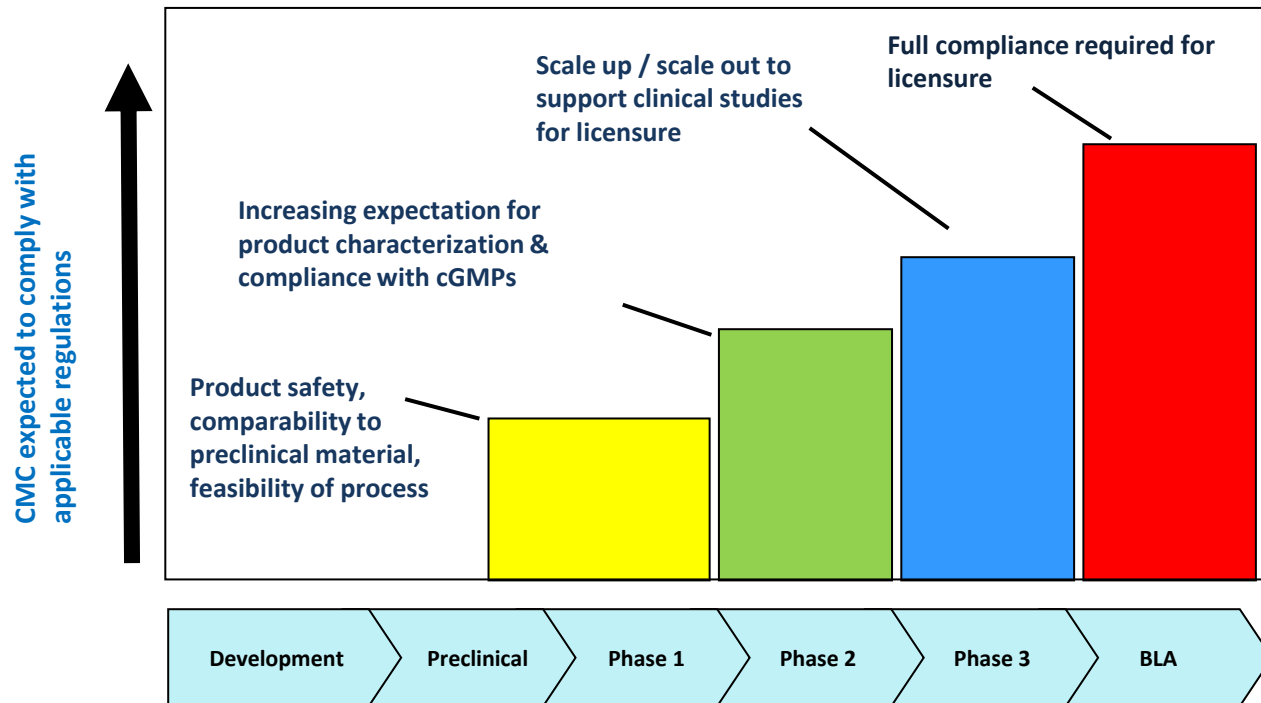


Which of the following statements is **NOT** true?

- A. Regulatory decision making involves a unique risk/benefit assessment for the disease, patient population, and agent(s) being evaluated.
- B. All CMC considerations for autologous and allogeneic cellular products are identical.
- C. Product variability arising from source materials is a major concern for CGT products.
- D. Multi-product manufacturing facilities require appropriate segregation of materials, equipment, and products.



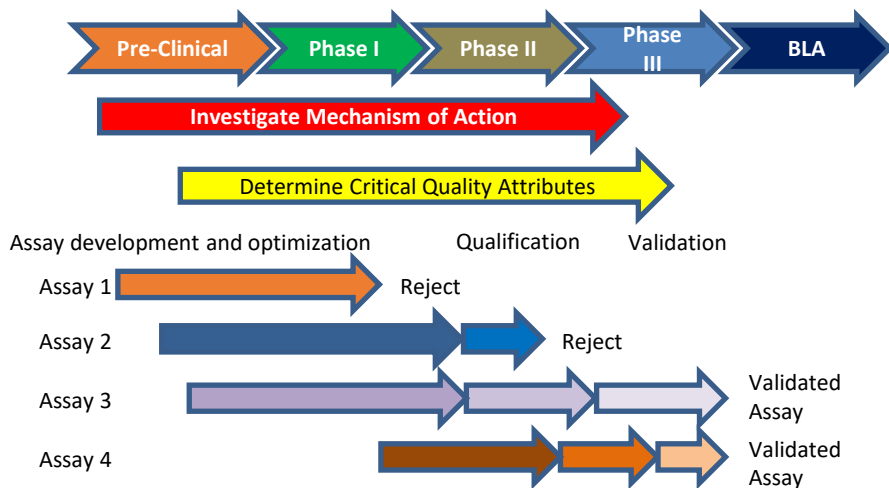
# CGT product development should progress in parallel with clinical development



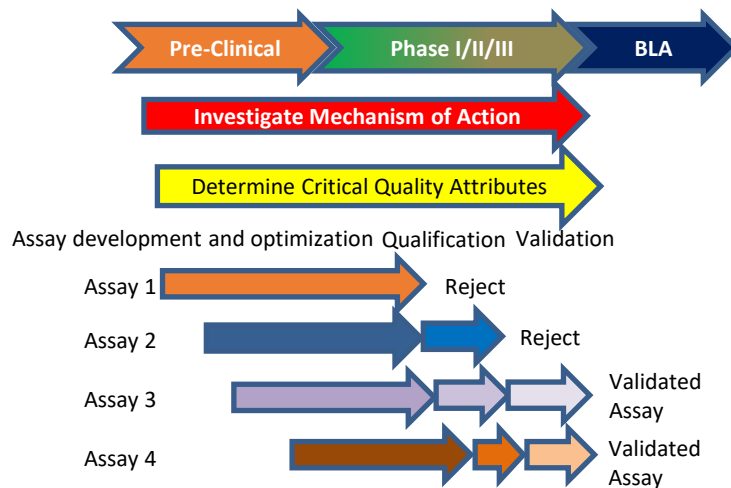
# Accelerated development: CMC challenges

- Promising clinical results and trend towards accelerated clinical studies...  
... giving less time for product development

## Traditional



## Accelerated



# Expedited development of promising treatments



## Expedited Programs

- Accelerated Approval (1992)
- Priority Review (1992)
- Fast Track (FT) Designation (1997)
- Breakthrough Therapy (BT) Designation (2012)
- Regenerative Medicine Advanced Therapy (RMAT) Designation (2016)

## FDA Guidance

[Expedited Programs for Serious Conditions—Drugs and Biologics \(2014\)](#)

[Expedited Programs for Regenerative Medicine Therapies for Serious Conditions \(2019\)](#)

# Regenerative Medicine Advanced Therapy (RMAT)

- **21st Century Cures Act: Title III, Section 3033**
  - Signed into law in 2016 and creates pathway for designation as a regenerative medicine advanced therapy
- **Definition of Regenerative Medicine Therapy:**
  - Cell therapy, therapeutic tissue engineering products, human cell and tissue products\*, or any combination product using such therapies or products
  - Combination product can be eligible for RMAT designation when the biological component provides the greatest contribution to the overall intended effects of the combination product
  - FDA interpretation of Section 3033 of the 21st Century Cures Act adds: “Gene therapies, including genetically modified cells, that lead to a sustained effect on cells or tissues”

\* Except for those regulated solely under section 361 of the PHS Act

# Comparison of expedited programs - Criteria

Accelerated Approval	Priority Review	Fast Track (FT)	Breakthrough Therapy (BT)	Regenerative Medicine Advanced Therapy (RMAT)
<p>-Serious condition</p> <p>AND</p> <p>- <b>Meaningful advantage</b> over available therapies</p> <p>- Demonstrates an effect on either: a <b>surrogate endpoint</b> or an <b>intermediate clinical endpoint</b></p>	<p>-Serious condition</p> <p>AND</p> <p>-Demonstrates potential to be a <b>significant improvement</b> in <b>safety or effectiveness</b></p>	<p>-Serious condition</p> <p>AND</p> <p>-<b>Nonclinical or clinical data</b> demonstrate the <b>potential to address unmet medical need</b></p> <p>Note: Information to demonstrate <i>potential</i> depends upon stage of development at which FT is requested</p>	<p>-Serious condition</p> <p>AND</p> <p>-<b>Preliminary clinical evidence</b> indicates that the drug may demonstrate <b>substantial improvement over available therapy</b> on one or more clinically significant endpoints</p>	<p>-Serious condition</p> <p>AND</p> <p>-It is a <u>regenerative medicine therapy</u></p> <p>- <b>Preliminary clinical evidence</b> indicates that the drug <b>has the potential to address unmet medical needs</b> for such disease or condition</p>

# Comparison of expedited programs - Features

Accelerated Approval	Priority Review	Fast Track (FT)	Breakthrough Therapy (BT)	RMAT
<p><b>Approval</b> based on surrogate or intermediate clinical endpoints</p> <p><b>Save valuable time</b> in the drug approval process</p> <p><b>Reduce waiting period for patients to obtain clinically meaningful benefit.</b></p>	<p><b>Shortened Review</b> Clock</p> <p>FDA will take action on an application <b>within 6 months</b> (compared to 10 months under traditional review)</p>	<p><b>Frequent meetings</b></p> <p><b>Eligibility for *:</b></p> <ul style="list-style-type: none"> <li>✓ Priority Review</li> <li>✓ Rolling Review</li> </ul> <p>*if relevant criteria are met</p>	<p><b>All FT Features, including:</b></p> <p>Actions to expedite development and review; Rolling review</p> <p>+</p> <p><b>Intensive guidance</b> on an efficient drug development program</p> <p><b>Organizational</b> commitment involving senior managers</p>	<p><b>All FT and BT Features, including</b> early interactions to discuss any potential surrogate or intermediate endpoints</p> <p>+</p> <p><b>Statute</b> addresses potential ways to support accelerated approval</p>

# CGT product expedited development: CMC expectations



- Clinical program advances rapidly for BT and RMAT products; timelines from early to late development may be compressed
- Accelerated clinical development should not change CMC and CGMP regulatory requirements and expectations
- Need to focus on all CMC and CGMP issues early if CGT product received a BT or RMAT designation: e.g., CQA/CPP, assay & process development/validation, raw material qualification and supply chain, major manufacturing change
- Planning for commercial scale manufacturing including comparability studies (when needed) should be conducted early (Phase 1/2)
- **Aligning CMC with clinical development is crucial**



# CGT product expedited development: CMC approach towards licensure

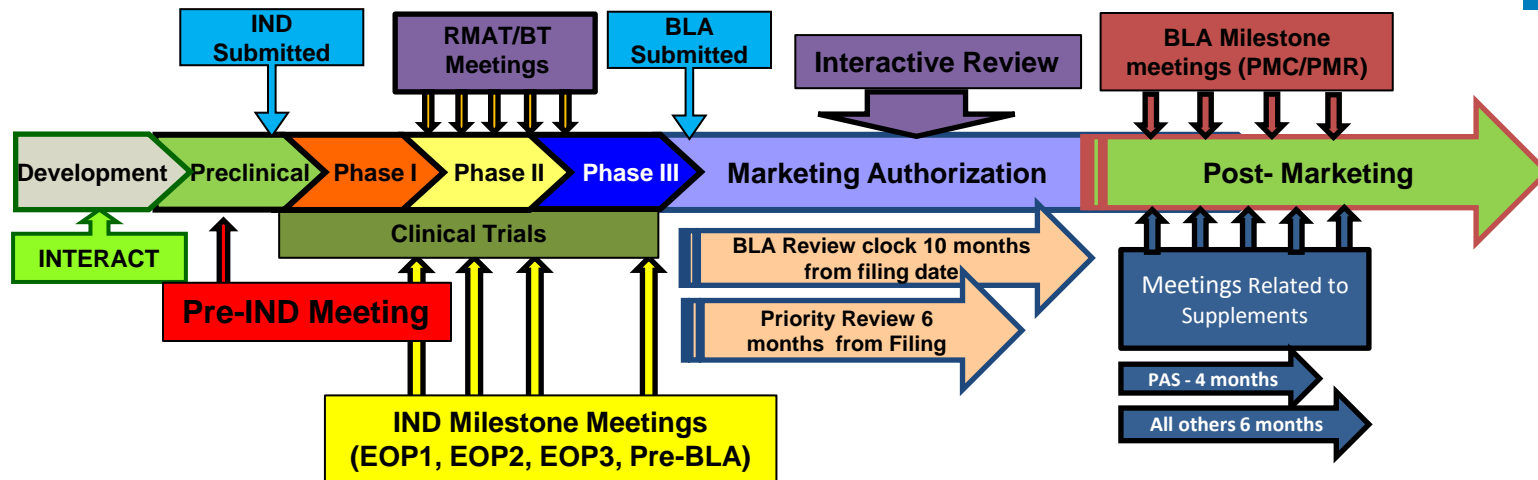


- **Essential goal:** Ensure the availability of a quality product that can be consistently produced at the time of approval
- **FDA may exercise some flexibility** *on the type and extent of manufacturing information* that is expected at the time of submission or approval for certain components to a certain degree. Case by case and dependent on:
  - Product characteristics
  - Seriousness of condition and unmet medical need
  - Manufacturing processes
  - Robustness of quality system
  - Strength of the risk-based quality assessment
- **Areas of potential flexibility**
  - Validation strategies, manufacturing scale-up/ scale-out strategies, use of post marketing commitments or post marketing requirements





# Opportunities for interaction with CBER/OTAT



- Novel products & rapid timelines: Increased need for feedback from FDA during CMC development
- Communication is especially useful throughout the product lifecycle for:
  - Topics that lack published guidance
  - Special circumstances
- Provide advice to specific queries (face-to-face, teleconference, or written response)
- Written minutes for formal meetings

# Challenge question #2



## Which of the following statements is true?

- A. CMC and GMP regulatory requirements for CGT products are waived for products with expedited development designations
- B. FDA always exercises flexibility on any type of manufacturing information that is expected at the time of BLA submission or approval
- C. A highly recommended product development strategy is to engage in CGT product development activities after clinical activity of the product is proven.
- D. The features of expedited development designations (i.e., FT, BT, RMAT) vary but always include frequent meetings with the FDA.

# Key CGT CMC guidance documents

## FINAL GUIDANCES

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (January 2020)
- Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus (RCR) during Product Manufacture and Patient Follow-up (January 2020)
- Guidance for Industry: Potency Test for Cellular and Gene Therapy Products. (January 2011)
- 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) (April, 2008)

## DRAFT GUIDANCES

- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial (September 2021)
- Human Gene Therapy Products Incorporating Human Genome Editing (March 2022)
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products (March 2022)

<https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances>

# OTAT guidance documents planned for 2022\*



- Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - Small Entity Compliance Guide; Guidance for Industry
- Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies; Draft Guidance for Industry and Staff
- Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry
- Human Gene Therapy for Neurodegenerative Diseases; Guidance for Industry
- Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry

\*Guidance Agenda: Guidance Documents CBER is Planning to Publish During Calendar Year 2022  
<https://www.fda.gov/media/120341/download>

# Summary



- The number of CGT products being evaluated clinically has reached an all time high
- CGT products are complex biologics requiring significant forethought regarding product development, particularly those in accelerated development
- Concurrent CMC development during clinical development of the product is crucial; seek FDA advice
- Investment of significant effort into understanding product attributes and analytical testing at all phases of clinical studies is crucial
- Product and process characterization and assay development should be started early and continued throughout the product lifecycle
- Process and analytical testing changes are expected during the lifecycle of a CGT product

**Plan ahead, try to resolve potential preclinical and CMC issues early in product development**

# Contact information

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- **Regulatory Questions:**

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- **OTAT Learn Webinar Series:**

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

- **CBER website:** [www.fda.gov/BiologicsBloodVaccines/default.htm](http://www.fda.gov/BiologicsBloodVaccines/default.htm)

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