



# Unlocking Next- Generation Therapies

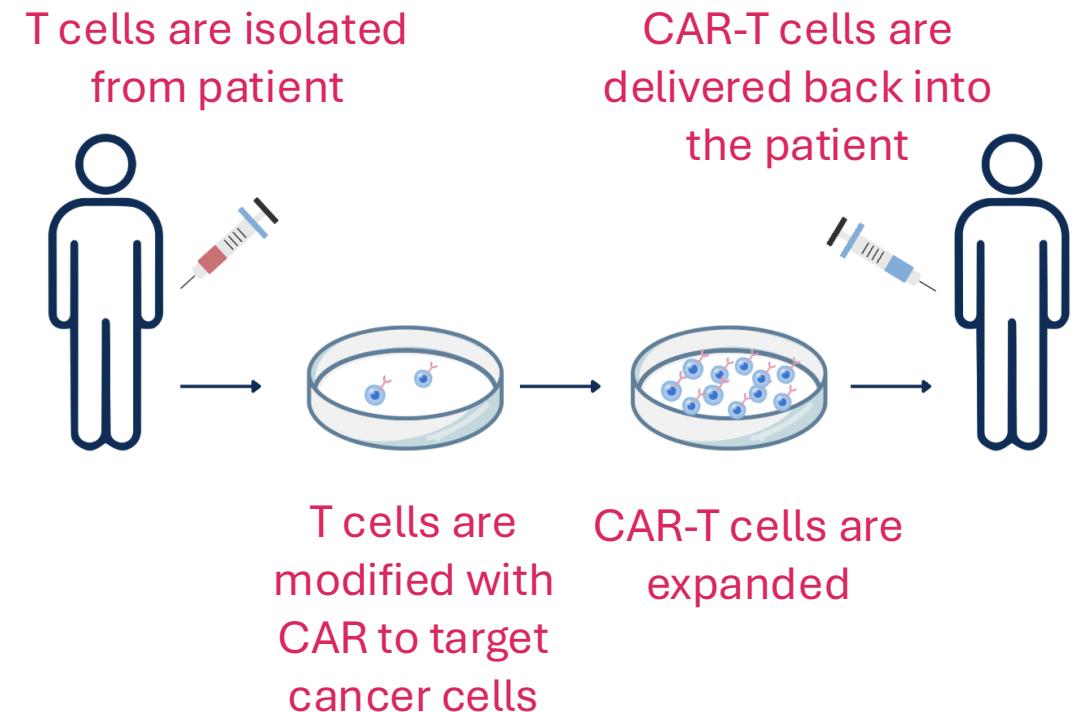
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# Overview of Cell and Gene Therapies

Cell and Gene Therapies (CGTs) involve modifying cells or introducing genetic material to treat or potentially cure a disease or cancer. They can be broadly grouped into three categories:

- **Cell therapy:** Uses living cells to treat patients, either from the patient (autologous) or a donor (allogeneic)
- **Gene therapy:** Introduces, removes, or alters genetic material (DNA or RNA) within a patient's cells to treat patients
- **Cell-based gene therapy:** Combines both approaches by using engineered cells to deliver genetic modifications (e.g., chimeric antigen receptor T-cell (CAR-T) therapy)

## CAR-T Therapy Paradigm



# Unique Features of CGTs and Their Implications

CGTs have unique product characteristics that influence trial design and regulatory expectations

## **Individualized therapies**

Many CGTs are manufactured for individual patients, creating challenges for applying standardized development approaches and complicating comparisons across programs

## **Protocol complexity**

Trial designs often require tailored approaches to elements such as eligibility criteria, dose escalation, bridging therapy, dose-limiting toxicity definitions, safety reporting, and stopping rules

## **Manufacturing and delivery constraints**

Autologous production timelines, supply chain logistics, and the need for specialized clinical sites introduce operational complexity

# The FDA has Demonstrated Openness to Flexibilities for CGTs

**Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products**

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**Draft Guidance for Industry**

**Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations**

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**Draft Guidance For Industry**

**Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause**

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**Draft Guidance for Industry**

**Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application**

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**Guidance for Industry**

## Select Guidance Documents

- **2023:** Manufacturing Changes and Comparability for Human CGT Products
- **2025:** Innovative Designs for Clinical Trials of CGT Products in Small Populations
- **2026:** Considerations for the use of the Plausible Mechanism Framework in Individualized Therapies
- **2026:** Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application

# Challenges with Current CGT Frameworks

## Translating FDA guidance documents into practice remains challenging due to:

- Variability in how existing frameworks and flexibilities are interpreted and applied across programs and development stages
- Uncertainty regarding whether frameworks fully align with the scientific and operational realities of CGT products

Delays in  
patient  
access to  
CGTs

More early-  
phase studies  
conducted  
outside the U.S.

Delays due to  
repeated review  
cycles and  
duplicative data  
generation

U.S. innovation  
and  
competitiveness  
at stake

Increased  
development  
costs

# Targeted Proposals to Advance CGT Development

	Early-phase clinical development	Manufacturing	Clinical trial design
Current Challenges	Gaps between existing guidance and practical application result in delays, repeated revisions, and duplicative data generation	Lack of clarity on when and how flexibilities apply can drive unnecessarily conservative CMC decisions (i.e., premature specification setting)	As CGTs transition into earlier treatment lines, evolving expectations introduce unique operational and design challenges
Targeted proposals	<ul style="list-style-type: none"> <li>Develop a common framework to reduce sponsor uncertainty, describe protocol elements to standardize and which warrant product-specific approaches</li> <li>Establish rapid, ad hoc feedback mechanisms</li> <li>Pilot streamlined oversight models for first-in-human development, including specialized IRBs and accreditation pathways for experienced centers</li> </ul>	<ul style="list-style-type: none"> <li>Establish a staged specification framework tied to development milestones, with phase-appropriate flexibility built in</li> <li>Develop a structured, lifecycle-based mechanism for prospectively managing CMC changes through development and commercialization</li> </ul>	<ul style="list-style-type: none"> <li>Clarify the contexts and characteristics in which alternative trial designs and comparator approaches are appropriate</li> <li>Explore novel early endpoints and clarify how CGT-specific factors weigh into benefit-risk determinations</li> </ul>

# Priority Areas for Ongoing Dialogue

- Which elements of early-phase CGT trial design have sufficient precedent to support a common framework?
- What would a CGT-specific CMC lifecycle mechanism look like in practice?
- What factors should guide the selection of appropriate trial designs (i.e., single-arm studies, novel endpoints, comparator choices) for specific CGTs?
- What policy opportunities could strengthen the U.S. as a global leader in CGT development and ensure patients have timely access to these therapies?

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**We thank the working group members for their expertise and contributions**