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Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products

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Outline

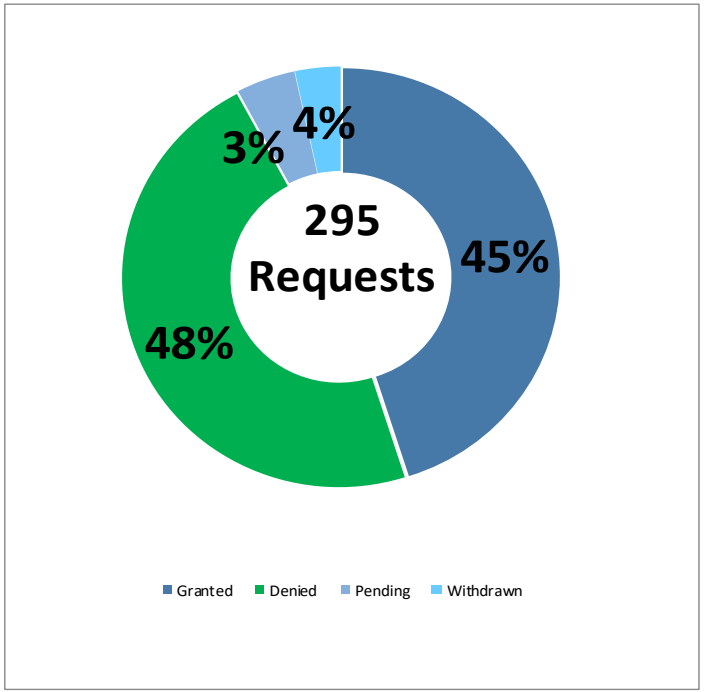
- Currently approved Cell and Gene Therapies
- Some vital statistics on expedited programs and types of Gene Therapies being developed
- Looking ahead to CAR T development
- FDA CAR T and related guidances
- The case for global regulatory convergence

U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)
- Lyfgenia (2023)
- Casgevy (2023, 2024)
- Lenmeldy (2024)
- Beqvez (2024)
- Tecelra (2024)
- Aucatzyl (2024)
- Kebilidi (2024)

Stem cell T cell Directly administered

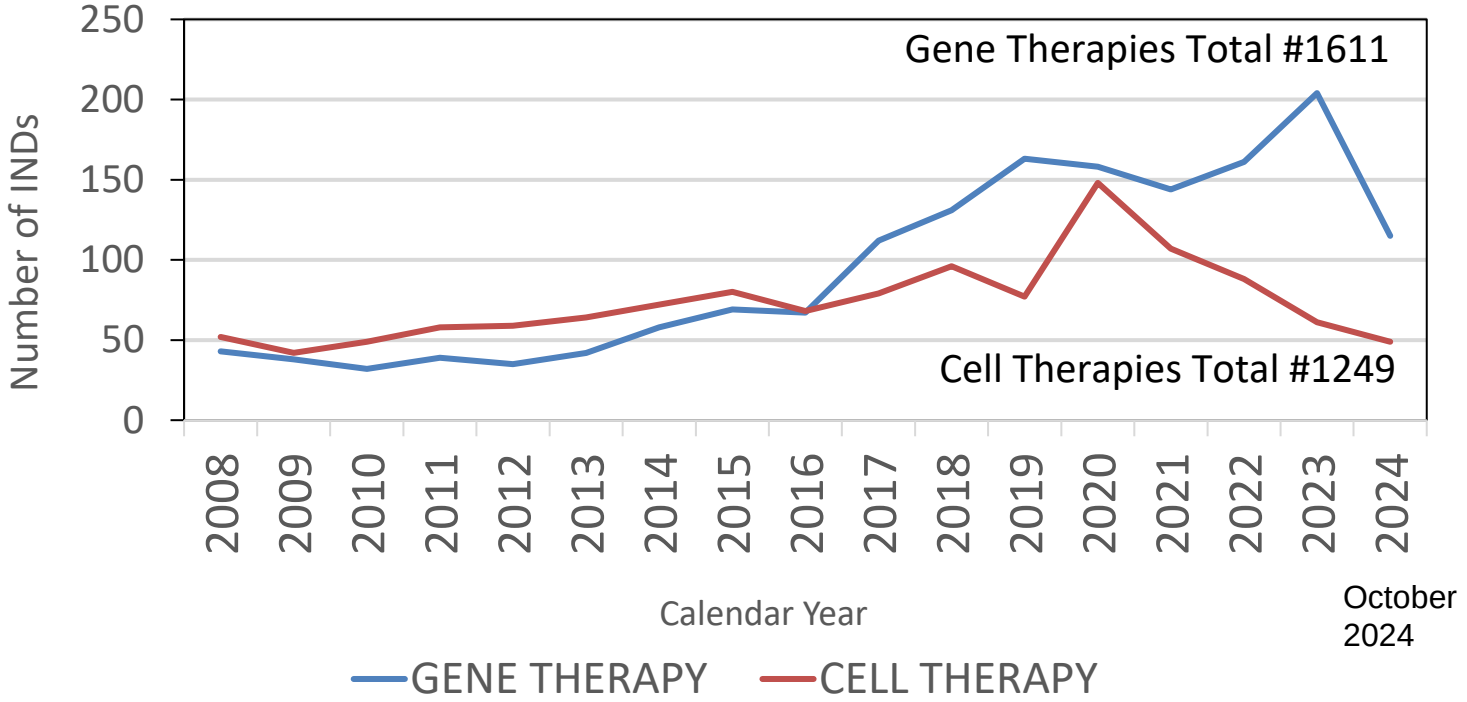
Regenerative Medicine Advanced Therapy (RMAT) Granted



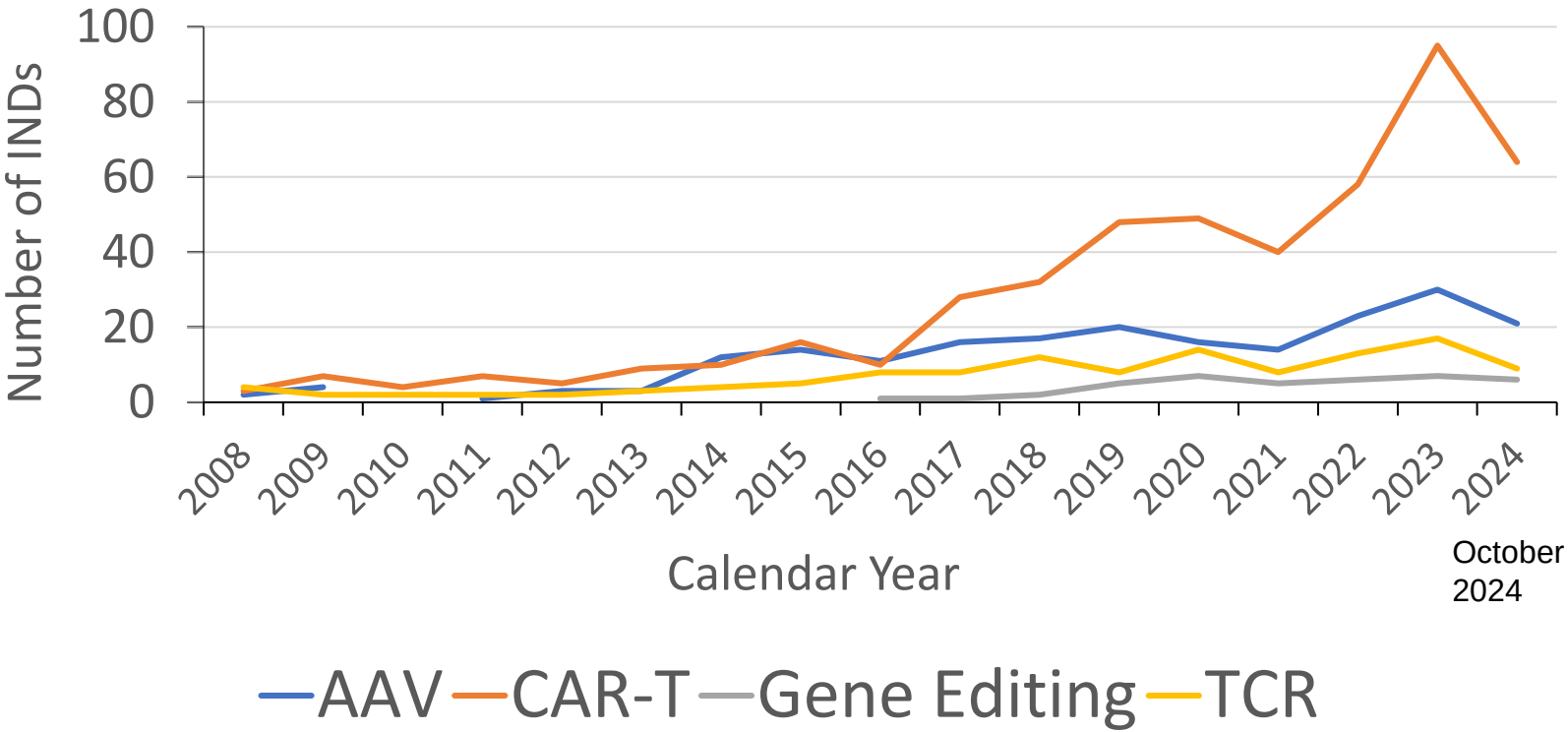
- **133 designations granted**
- 53 of the 133 RMAT granted products have Orphan Product designation
- 50 of the 133 RMAT granted products have Fast Track designation

Cell and Gene Therapies: New INDs per year

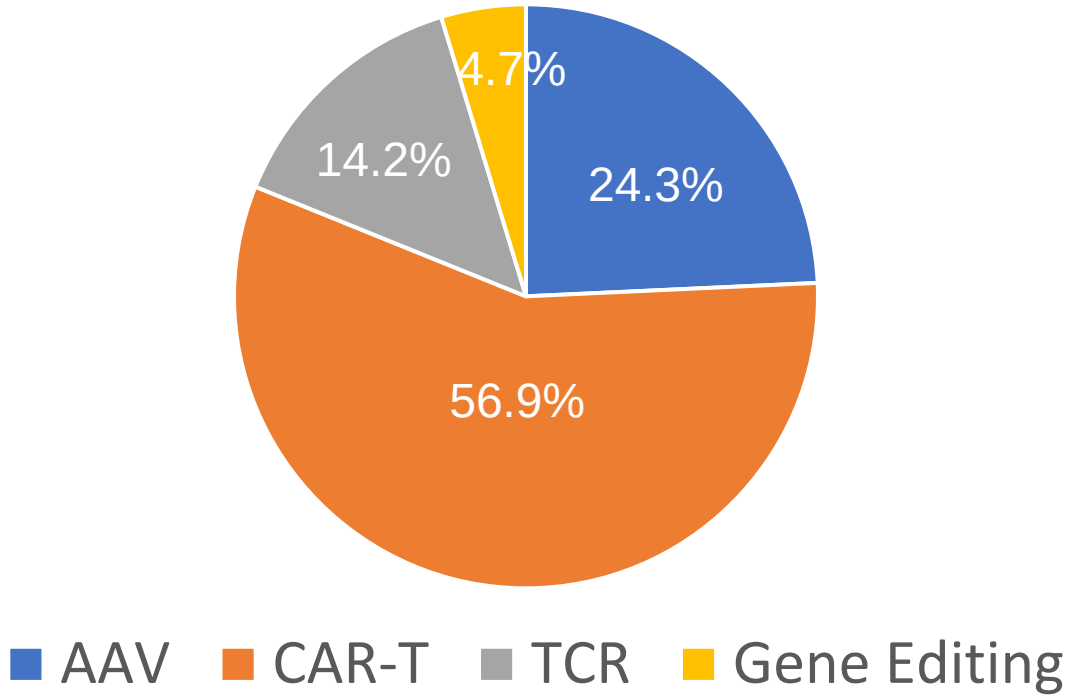
Excluding expanded access



Total GT INDs Per Year by Type



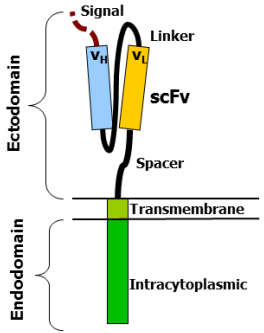
Total INDs by GT Types



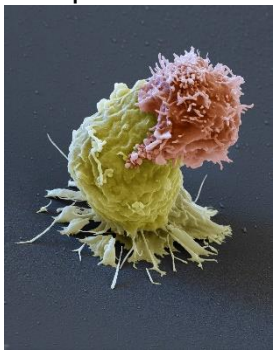
Current Challenges

- Gene therapy is currently at a critical juncture due to a combination of factors
  - Manufacturing challenges
  - Clinical development timelines
  - Different global regulatory requirements

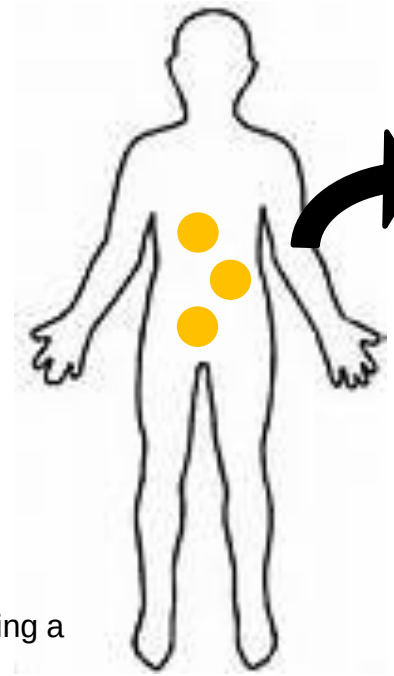
Chimeric Antigen Receptor (CAR T) Cell Therapy



Chimeric antigen receptor structure



A CAR-T cell (pink) attacking a cancer cell (yellow)



Patient

T cell activation and transduction with gene transfer vector

Apheresis Product

Expand in culture CD3/CD28 beads + IL-2 / IL-15

Dose formulation Product testing

Gene modified T cell Infusion

Patient may receive pre-conditioning chemotherapy prior to infusion
Sometimes cytokine support (IL-2) post-infusion

Looking Ahead at CAR T Development

Comparison of CAR T-Cell Therapies

Allogeneic CAR T Cells

❑ **Pros:**

- Off-the-shelf availability
- Reduced lot-lot variability
- Reduced time to patient
- Likely reduced cost
- Potential for broader application

❑ **Cons:**

- Risk of Graft-Versus-Host Disease (GVHD)
- Complexity in matching
- Immune rejection
- Limited persistence

Autologous CAR T Cells*

❑ **Pros:**

- Higher persistence
- Personalized treatment
- Established success in the field

❑ **Cons:**

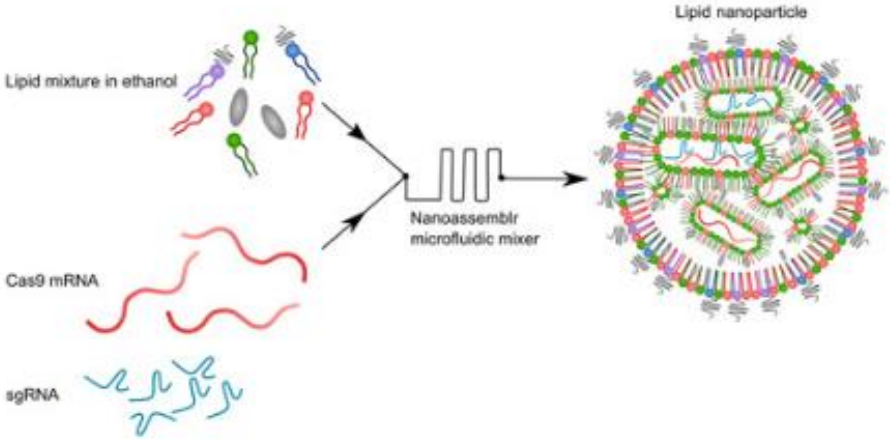
- Increased time to patient
- Likely higher costs
- Limited availability for urgent cases
- Potential issues with cell quality

*Currently approved products

CAR-T Cells Produced *in vivo*

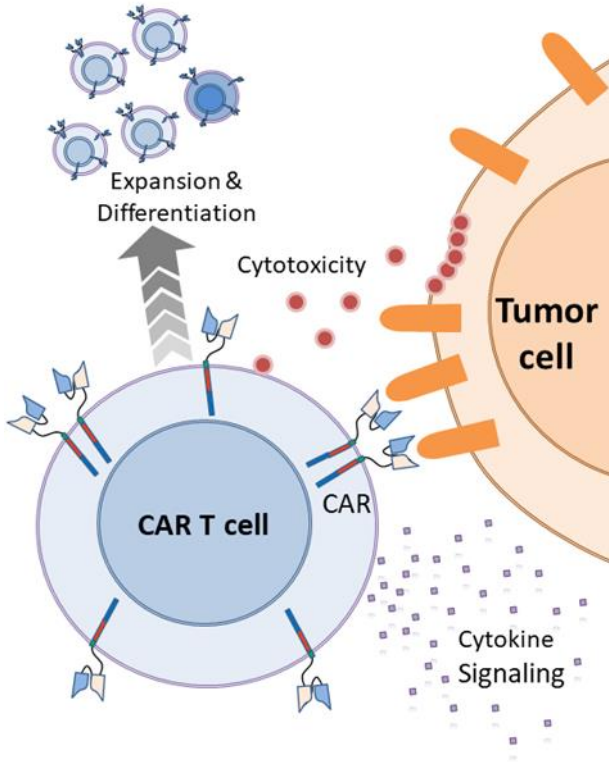
- Developments in targeting nanoparticles may facilitate the modification of T cells *in vivo*
  - Could be associated with a marked reduction in complexity and cost of therapy
- Site specific insertion of sequence may ultimately also overcome some current adverse effects
  - Potentially applicable to ex vivo approach as well

Promise of the mRNA Platform



From: Rosenblum et al., Sci. Adv. 2020; 6:eabc9450.

FDA CAR T and Related Guidances



History of CAR T Guidance

- This guidance focuses on ex vivo modified CAR T cells for oncology indications (including solid tumors and hematologic malignancies)
- The recommendations in this guidance were based on FDA's experience with CAR T cell development, including with approved CAR T cell therapies

Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products | FDA

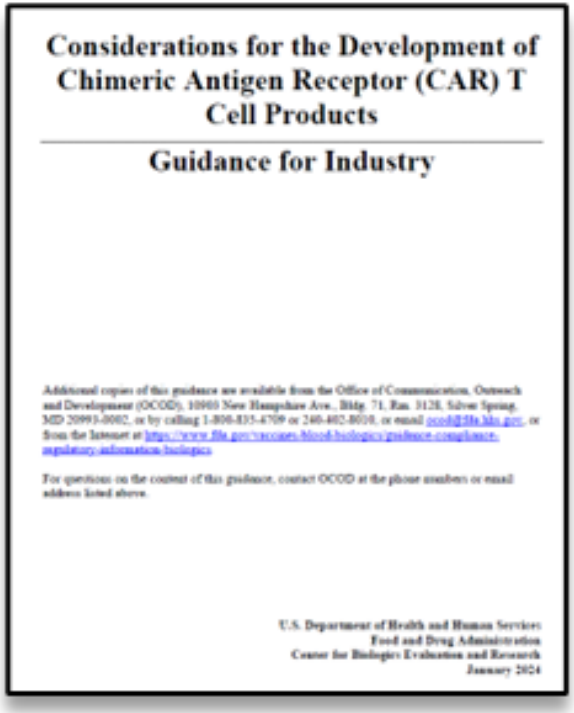
- Draft posted for comment
  - March 15, 2022
- Comment period closed
  - June 15, 2022
- Final guidance published
  - January 29, 2024

Related FDA Guidances

- This guidance addresses considerations specific to CAR T cell products and is not designed to be a stand-alone guidance
- Please refer to the additional guidance documents on cell and gene therapies available from FDA's website: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances.

Outline of CAR T Guidance

- Background
- General considerations for CAR T cell design and development
- CMC recommendations
- Nonclinical recommendations
- Clinical recommendations
- Questions and Answers



Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2024

CMC Recommendations

A. Vector Manufacturing and Testing
B. Collection, Handling, and Testing of Cellular Starting Material (including leukapheresis material)
C. CAR T Cell Manufacturing and Testing
    1. CAR T cell manufacturing process control
    2. CAR T cell analytical testing
    3. Labeling for CAR T cells
D. Managing Manufacturing Changes and Assessing Comparability During the CAR T Cell Product Lifecycle
    1. Change management
    2. Comparability study design
    3. Single-Site or Multisite CAR T Cell Manufacturing

CMC Recommendations (cont.)

Collection, Handling, and Testing of Cellular Starting Material

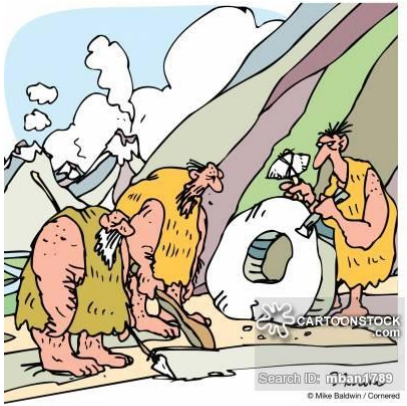
- Collection of the leukapheresis starting material should be conducted in accordance with the regulations in 21 CFR part 1271 (Note: Autologous leukapheresis starting material does not require a donor eligibility determination)
- **Cellular starting material can represent a major source of lot-to-lot variability in CAR T cell quality and function**
  - Describe procedures used for handling the leukapheresis starting material from collection to the start of the manufacturing process
    - should include any wash steps or cryopreservation procedures
    - adequate control of the leukapheresis starting material during shipping to the manufacturing facility
  - probability of manufacturing success may be increased by establishing acceptance criteria for the leukapheresis starting material
- Chain of Identity (COI) starts at time of leukapheresis collection

Manufacturing Changes Are Inevitable

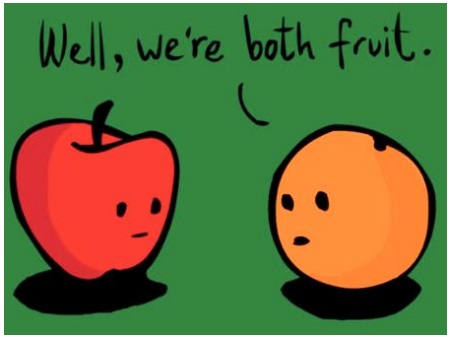
Some examples include:

- Scale-up/scale-out, new manufacturing site, new analytical assay
- Reacting to manufacturing problem or contamination
- Reagent or material is no longer available or in short supply
- Improve product quality based on new scientific or clinical information
- Process improvements (e.g., more efficient or streamlined process, better impurity profile, etc.)
- Cost effectiveness
- Cell bank has expired or been exhausted

Changes can occur at any point in the product lifecycle, but one needs to ensure that the change does not negatively impact product quality as it relates to S&E



"What's with kids nowadays? Walking upright's not good enough for you?"



CMC Recommendations (cont.)

CAR T cell manufacturing process control

- Well-controlled via the use of quality materials, control of process parameters, in-process testing, and testing of intermediates and the final product for CQAs
- Manufacturing should be conducted by using qualified aseptic processing under CGMP requirements
- Generally, starting material from a healthy donor is appropriate for manufacturing process developmental batches; consider disease state, prior treatment, or other inherent patient characteristics

Managing manufacturing changes and assessing comparability during the CAR T cell product lifecycle

- Comparability supports manufacturing changes and multi-site manufacturing
- Refer to: Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products: DRAFT Guidance for Industry

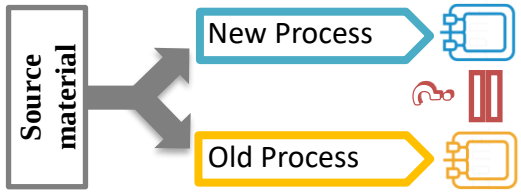
Products derived from a variable cellular starting material

Donor-derived cells are highly variable

This results in variable product attributes, which can make it difficult to evaluate how manufacturing changes affect product quality

Split-source material study design and paired statistical analysis may help

This study design can minimize the effect of source material variability

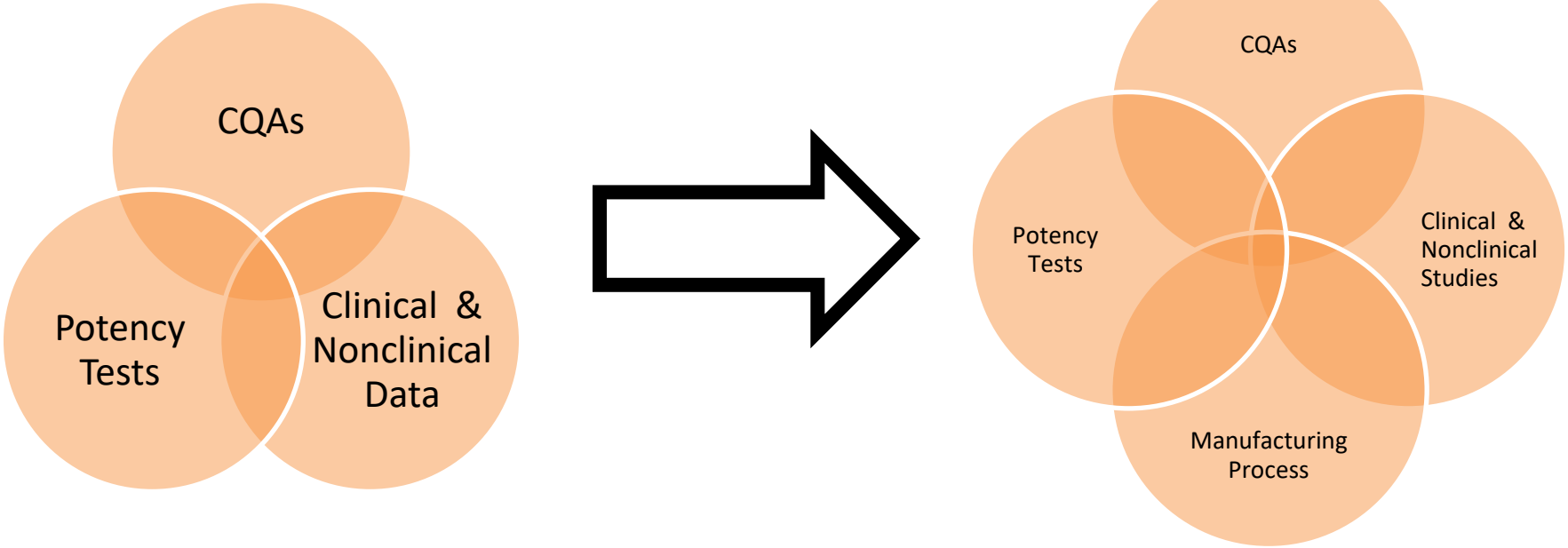


When manufacturing product for comparability studies:

Best to use the same type of source material as the clinical product

But may be able to use other material if justified
(for example, cells from healthy donors)

New FDA Draft Potency Guidance: Shift in Focus



Key Highlights from New Draft Guidance - *Potency Assurance for Cellular and Gene Therapy Products*

1) Emphasis on bioassays

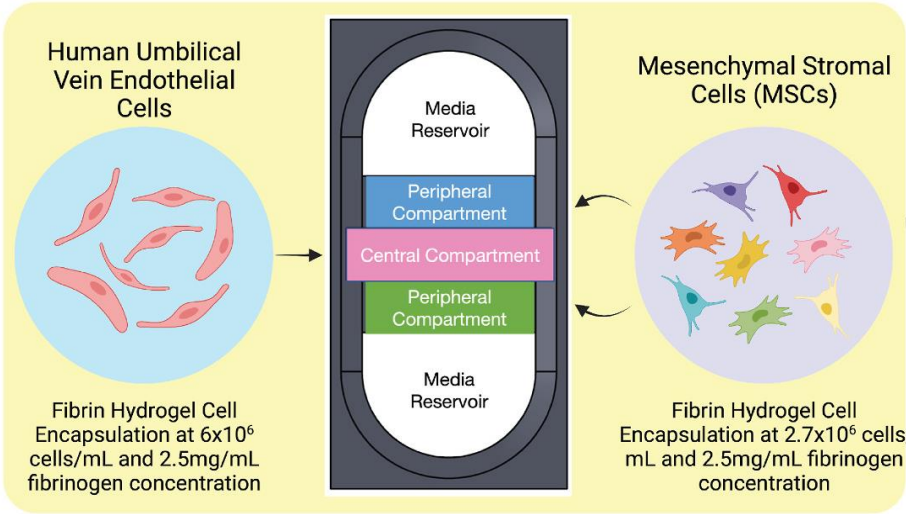


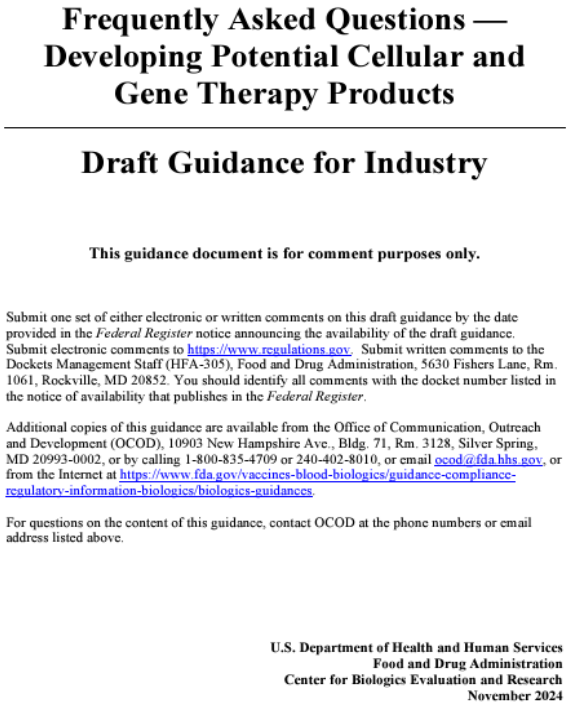
Image adapted from Lam J, Lee B, Yu J, et al. A microphysiological system-based potency bioassay for the functional quality assessment of mesenchymal stromal cells targeting vasculogenesis. *Biomaterials*. 2022;290:121826. doi:10.1016/j.biomaterials.2022.121826

2) Concepts for holistic approach

Frequently Asked Questions — Developing Potential Cellular and Gene Therapy Products

Draft Guidance for Industry

- Interacting with FDA
  - IND submission & Quality (info to include in an IND)
  - Meeting types (Type D, INTERACT vs. pre-IND, etc.)
- Product development considerations
  - donor eligibility (e.g., autologous vs. allogeneic)
  - Product characterization vs. release testing
  - Identification of CQA
  - Process validation recommendations
  - Manufacturing changes
- Series of recommendations for non-clinical and clinical studies



Frequently Asked Questions — Developing Potential Cellular and Gene Therapy Products

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2024

Global Regulatory Convergence

Global Harmonization Opportunities Underway

Collaboration on Gene Therapies Global (CoGenT Global) Pilot

- Initial participation by Standing Regulatory Members of ICH
- Partners may participate in internal regulatory meetings and meetings that include the sponsor
- Specific regulatory reviews are shared and discussed with partners
- All meetings conducted and information shared under strict confidentiality agreements
- Goal is to increase the efficiency of the regulatory process, reducing time and cost for agencies and sponsors

www.fda.gov 24

World Health Organization

ICH Cell and Gene Therapies Discussion Group (CGTDG)

ICH harmonisation for better health

Endorsed by the ICH Management Committee on 12 May 2023

ICH Remit Paper

ICH Cell and Gene Therapies Discussion Group

General Description

The ICH Cell and Gene Therapies Discussion Group (CGTDG) will serve as a technical discussion forum for issues related to ICH harmonization efforts in the field of Cell and Gene Therapies (CGT) products. The CGTDG will develop a holistic CGT roadmap within the scope of modalities identified below, including prioritization of areas of most need for harmonization whereby technical consensus can be achieved with specific recommendations for new guideline development or revisions to existing ICH Guidelines.

As acknowledged by the ICH Management Committee (MC), there is a developing need for regulatory harmonization on topics related to CGT products, an emerging field with an expanding global clinical development landscape and a significant promise in the treatment and cure of debilitating and life-threatening diseases. The overall aim of CGTDG is to develop a strategic framework to address the future harmonization needs for this emerging field, and provide recommendations to the MC in guiding ICH activities to address these technological advancements. It is expected that the ICH CGTDG will work in close collaboration and coordination with IPRP and WHO CGT focused groups to ensure a holistic approach to harmonization efforts, and equally minimize any duplicative efforts.

The CGTDG will operate in line with the applicable ICH procedures, similar to other ICH Discussion Groups, under the oversight of the ICH MC, and reporting to the ICH Assembly. As the remit of ICH is to harmonize technical standards, the CGTDG is tasked to focus on technical and scientific aspects and ensure that ICH Guidelines are kept up-to-date with the evolution of science.

Scope of Activities

Given the scientific complexities and diverse array of CGT modalities, it is proposed that the CGTDG focus its initial scope on CGT modalities of relatively high maturity, whereby greater scientific and regulatory expertise have already been achieved. The selection of such modalities can be linked to classes of products that have achieved global marketing authorization or those modalities that are prominent in global clinical development programs. The proposed modalities within scope are:

- Ex-vivo genetically modified chimeric antigen receptor engineered T cell (CAR-T cell), including both autologous and allogeneic;
- In-vivo viral vector-based gene therapy (e.g., AV, AAV, …).

The initial work of the CGTDG will be to drive alignment on high level principles within selected modalities where baseline consensus can be achieved. The CGTDG will:

- Review areas that will benefit from ICH harmonization, and prioritize those areas of most need to enable future ICH work in a staggered approach;
- Assess current ICH Guidelines for their applicability to CGT products, and;
- Make specific recommendations regarding the development of new ICH guidelines for CGT products and/or revisions to existing guidelines as deemed necessary.

IPRP International Pharmaceutical Regulators Programme

- Gene Therapy Working Group (GTWG)
  - Objectives: [...] to maintain the international networking forum in order to discuss emerging scientific developments and concerns for the regulation of GT products and to share regional updates in guidelines, science, and regulation of GT products.
  - Publication of "*International Regulatory Frameworks for Cell and Gene Therapies*" (11 Aug 2021) https://admin.iprp.global/sites/default/files/2021-09/IPRP_CTWG-GTWG_Frameworks_2021_0811_1.pdf

- Cell Therapy Working Group (CTWG)
  - The primary goals of the Working Group are information sharing and regulatory convergence.
  - Objectives: (1) open discussion and sharing of best practices for the regulation of cell and tissue-based therapies; (2) support harmonization initiatives such as APEC; (3) refer topics to appropriate organizations such as ICH, PIC/S, PANDRH, WHO.

Summary

- CBER is committed to advancing the science and regulatory evaluation of Cell & gene Therapies
- Through various initiatives underway, the center aims to assist developers and manufacturers of CGTs with improving the efficiency of the development processes, as well as enhance use of expedited review process, ultimately providing patients with earlier access
- Global regulatory convergence could help facilitate commercial availability and pave the way for the use of Cell & Gene Therapies world-wide


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