Regulatory Considerations for CAR T Cell Development

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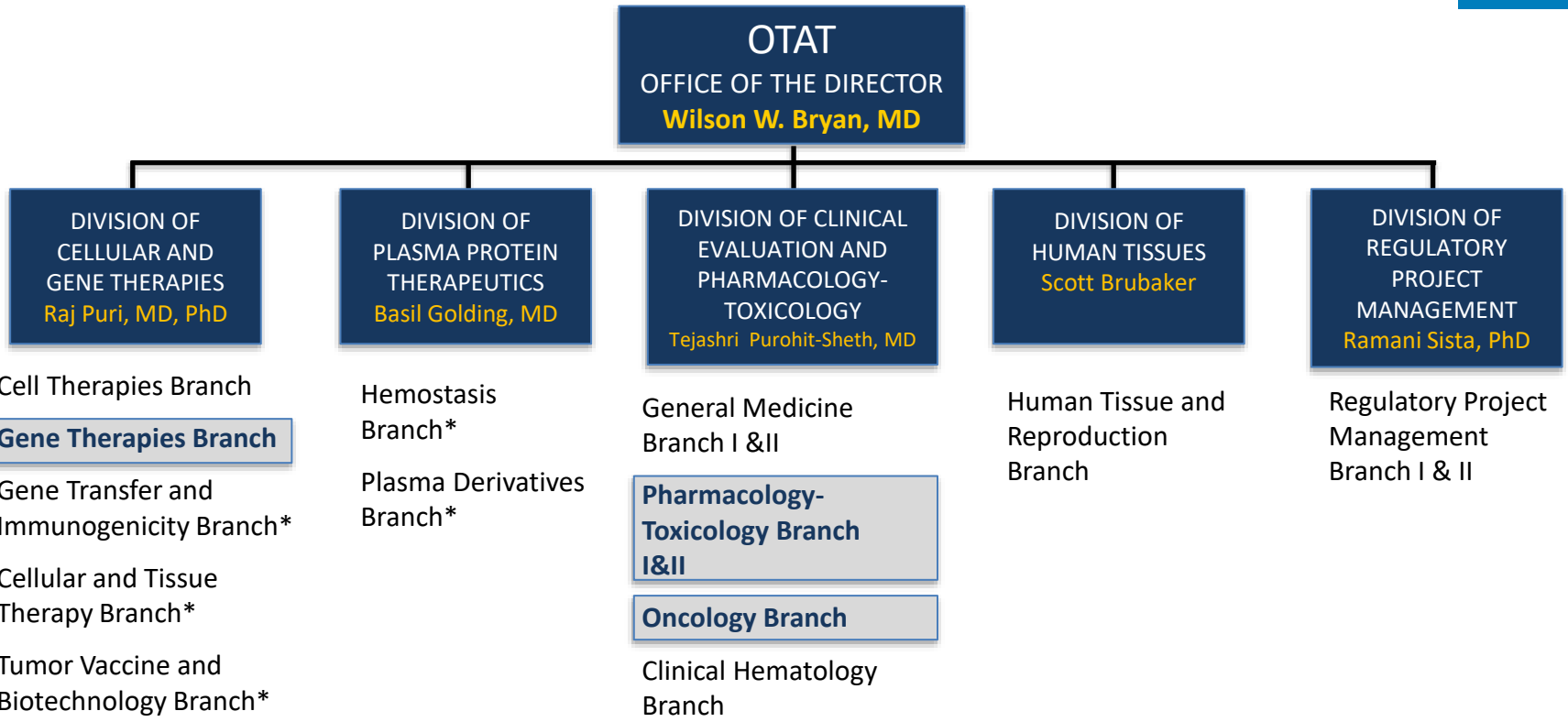


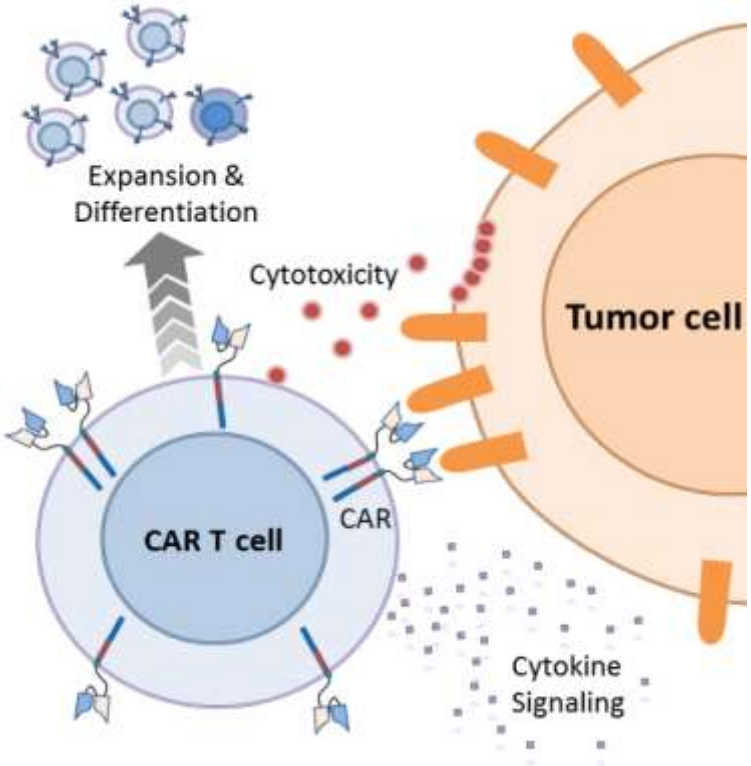
*Units that include lab research

Diversity of OTAT-Regulated Products

- **Gene therapies (GT)**
  - Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)
- **Stem cells/stem cell-derived**
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)
- **Products for xenotransplantation**
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Anti-toxins
  - Venom antisera for scorpions, snakes, and spiders
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

Chimeric Antigen Receptor (CAR) T cells

- Human Gene Therapy
- Targets cell surface antigen
  - Not restricted by HLA
  - Retains endogenous TCRs; can be removed by genome editing
- Promotes cell expansion and differentiation
- Activates T cell signaling
- 4 FDA-licensed products
- Regulatory principles can be applied to other ex vivo modified cells

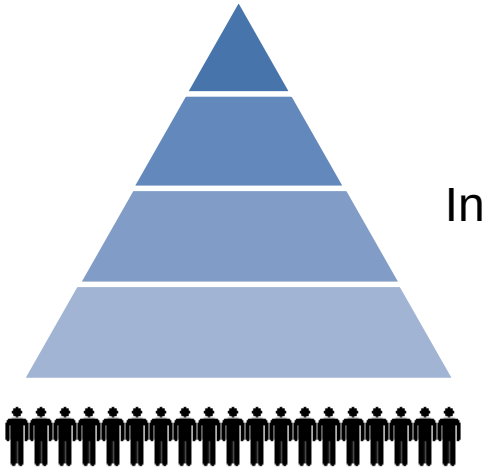


Different Manufacturing Paradigms

11% of CAR T cell INDs are for allogenic products as of 1/1/2021

Allogeneic CAR T cells

1 product lot



Many patients

Raw materials

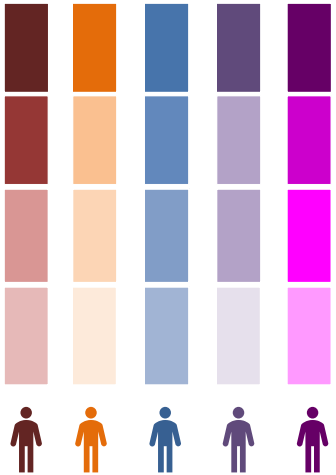
cGMP Manufacturing

In Process and Lot Release Testing

Distribution

Autologous CAR T cells

1 product lot



One patient

How to know what you need to start?

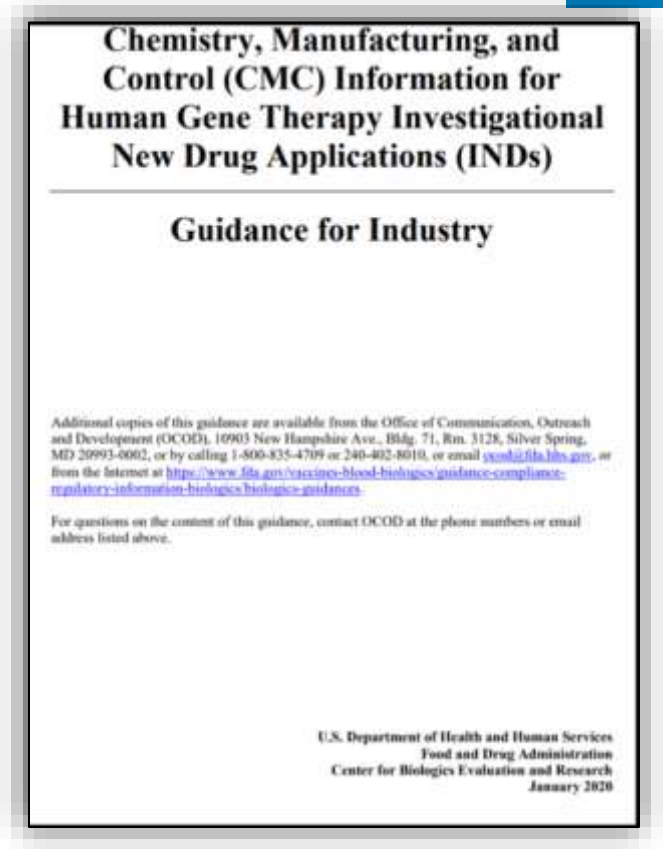
Available Now:

- Cellular & Gene Therapy-specific Guidances

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

Coming Soon:

- Guidances focused on CAR T cells and Genome Editing



Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

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/biologics-guidances.

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
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Options for Early Engagement with CBER

Informal regulatory advice

Formal regulatory advice

CATT

INTERACT

Pre-IND Meeting
CMC:
- Manufacturing
- Lot Release

P/T:
- Animal Safety & Immunogenicity

Clinical:
- Phase 1 protocol

EOP2 Meeting
- Phase 3 protocol
- Phase 1 & 2 data
- Update on manufacturing & lot release

Pre-BLA Meeting
- Clinical data summary
- Manufacturing & lot release
- BLA Outline

CATT = CBER Advanced Technology Team
IND = Investigational New Drug
BLA = Biologics License Application

Ensuring CAR T Cell Product Quality

- Suitable qualification of starting materials & components
- Development of a well-defined process with controls
- Process qualification (e.g., engineering runs)
- CGMP manufacturing
  - Guidance for Industry: CGMP for Phase 1 Investigational Drugs (2008)
  - Later phase per full CGMP
- Informative product testing & characterization

Starting Materials, Reagents, & Components

- List all manufacturing reagents and provide quality documentation
  - Select the highest quality reagents (e.g., media, serum, growth factors, stimulation beads, stimulating antigen) available and establish vendor/reagent qualification program
  - Cross reference information if a Master File exists

    Draft Guidance for Industry: Drug Master Files (2019)
- Establish acceptance criteria for reagents, including those used for analytical purposes
- Ensure sufficient supplies of critical materials

Allo CAR T Cells: Donor Testing and Screening

- Required for human cells, tissues, or cellular or tissue-based products when source material is collected from allogeneic human donors (21 CFR 1271)
- Donor blood testing & screening (e.g., medical questionnaire) must be performed to determine eligibility
- CBER guidance documents provide additional detail on:
  - What infectious agents must be tested
  - When donors must be tested
  - How they are tested and the types of test kits
  - Where the testing must take place
- Requirements are the same regardless of country of origin:
  - FDA-licensed test kits
  - CLIA certified labs or equivalent as determined by the Centers for Medicare and Medicaid Services (CMS)
  - Perform all the nucleic acid and antibody-based testing required

Cellular Starting Material Qualification

- Safety testing
  - Sterility and mycoplasma recommended
  - Allo: may require additional relevant human pathogens not included in donor eligibility testing
- Establish acceptance criteria for incoming material
  - Minimum cell number, % $CD3^+$, viability
- Conduct additional characterization studies
  - Phenotypic analysis (e.g., % and absolute number of $CD4^+$ and $CD8^+$, NK, monocytes, B cells etc.)
  - May inform process development (e.g., need for cell selection)

Vector quality impacts CAR T cell quality

- Various vector types: plasmid, retrovirus/lentivirus, AAV
- Information provided in a complete Drug Substance (DS) section
- Manufactured according to CGMPs
- Master and working cell banks should be fully characterized and tested
- Release testing completed prior to CAR T cell manufacture and stability program established
- Using standard amount of vector (e.g., MOI) is a critical CAR T process control

Parameter	Tests
Safety	Sterility, Endotoxin, Mycoplasma, *in vitro* adventitious agents, Replication competent retrovirus/lentivirus if applicable (End of Production (EOP) cells and vector supernatant)
Identity	Presence of transgene sequence (PCR, Southern blot etc.)
Purity	Process and product-related impurities (residual BSA, antibiotics, host cell DNA, etc.)
Dose	Vector concentration/titer (e.g., transducing units/ml)
Potency	Cytokine production, tumor cell killing, gene expression, phenotype, etc.

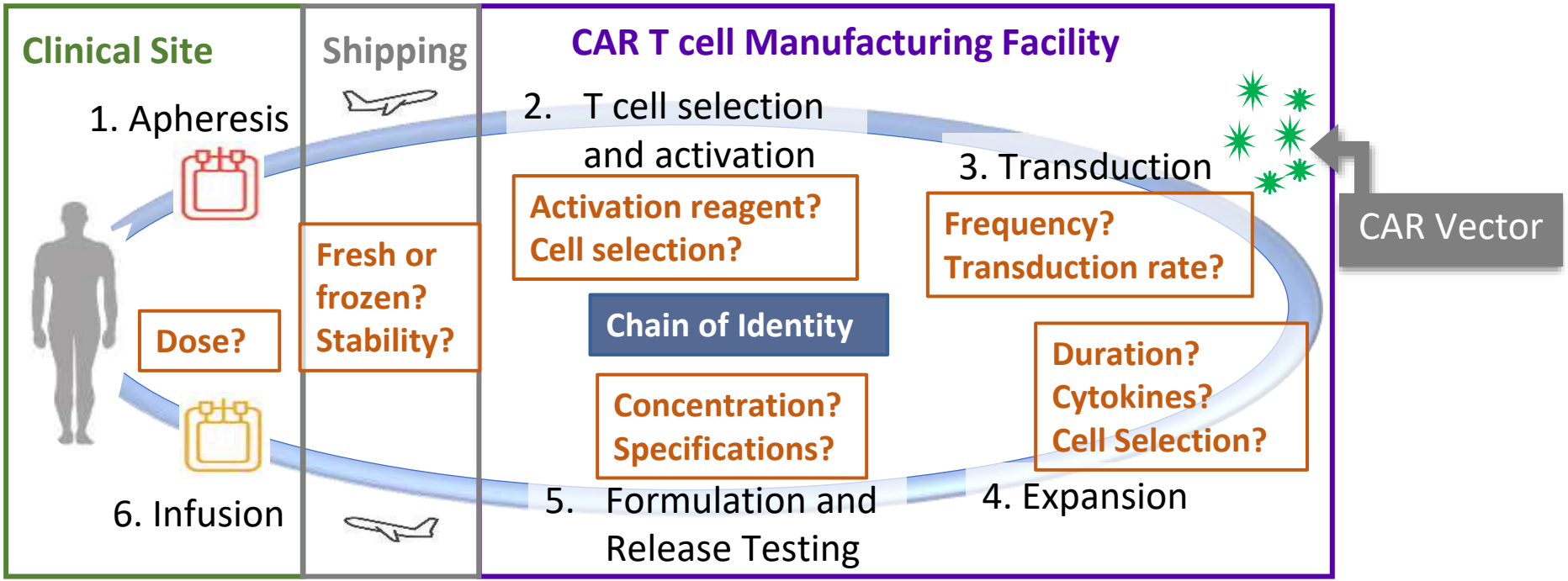
Genome Editing (GE) Components

- GE is one of many ways to block or knock-out TCR in allo-CAR T cells
- Nuclease, targeting elements, and donor template are considered critical components
- Include details on component design, manufacture and testing (identity, purity, activity) in DS section
- If components are modified during the product life cycle, comparability studies may be necessary
- Recommend INTERACT and/or preIND meeting

Ensuring CAR T Cell Product Quality

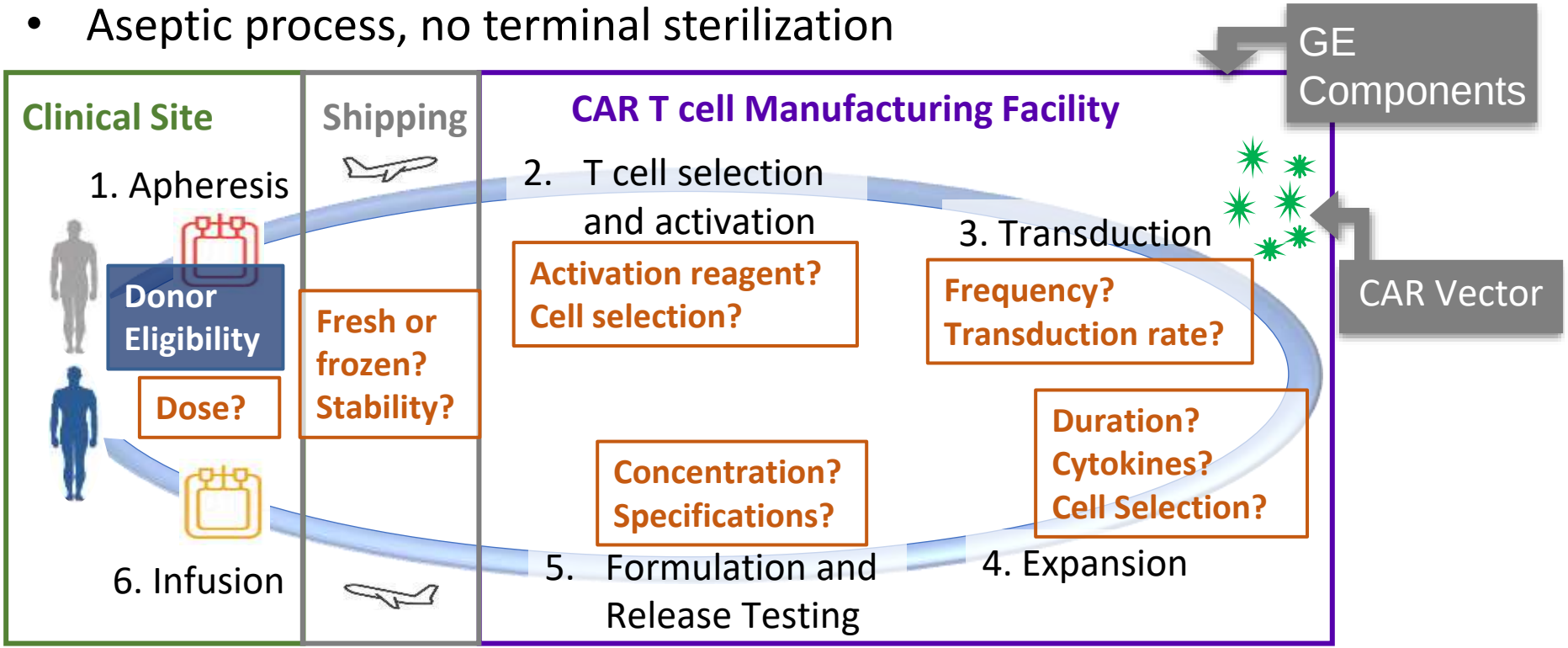
How does each step affect the Auto DP?

- Main components: patient's cells & CAR vector
- Aseptic process, no terminal sterilization



How does each step affect the Allo DP?

- Main components: donor cells, TCR disruption, & CAR vector
- Aseptic process, no terminal sterilization



Ensuring CAR T Cell Product Quality

GT Assay Development

For INDs, **sufficient information is required at each phase of an investigation to ensure proper identity, quality, purity, strength, and/or potency**. The amount of information on analytical procedures and methods suitability will vary with the phase of the investigation.

- Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics (2015)

Early Phase Studies:

- Qualify assays used for product release and stability testing (suitable for the intended purpose)
- Develop characterization assays
- Explore a variety of product characteristics

Late Phase Studies:

- Validate critical assays (potency and dose)
- Lot release assays:
  Validation planned or completed
- Characterization assays:
  Developed & qualified
- Reference standards & controls:
  Developed & qualified

CAR T Cells: Lot Release Testing

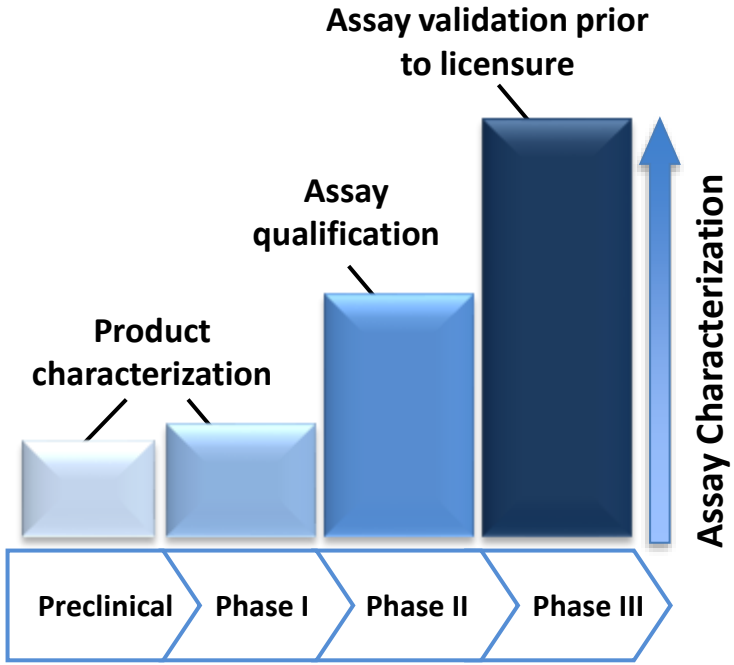
Parameter	Tests
Safety	Mycoplasma, Sterility, Endotoxin, replication competent virus (if applicable) Viability (≥ 70%) Vector copy number per transduced cell (integrating vectors)
Identity	Presence of transgene (e.g., PCR/flow cytometry specific for CAR)
Purity	Absence of process & product-related impurities (e.g., BSA, beads, reagents etc.) T cell purity Transduction efficiency (% CAR^+ cells)
Dose	Number of viable CAR expressing T cells
Potency	Cytokine production, tumor cell killing, phenotype, etc.

CAR T Cells: Lot Release Testing

Parameter	Tests
Safety	Mycoplasma, Sterility, Endotoxin, replication competent virus (if applicable) Viability (≥ 70%) Vector copy number per transduced cell (integrating vectors) *Allo: Number of αβ T cells (e.g., < 1x10^4/kg for starting dose, no more than 7x10^4/kg for high dose)* *GE: Absence of cytokine independent growth* *GE: Frequency of off-target editing, frequency of translocations*
Identity	Presence of transgene (e.g., PCR/flow cytometry specific for CAR)
Purity	Absence of process & product-related impurities (e.g., BSA, beads, reagents etc.) T cell purity Transduction efficiency (% CAR$^+$ cells) *GE: Sequence insertion frequency (for HDR)* *GE: Frequency of on-target editing (can also be part of identity testing)*
Dose	Number of viable CAR expressing T cells
Potency	Cytokine production, tumor cell killing, phenotype, etc.

CAR T Cell Characterization Testing

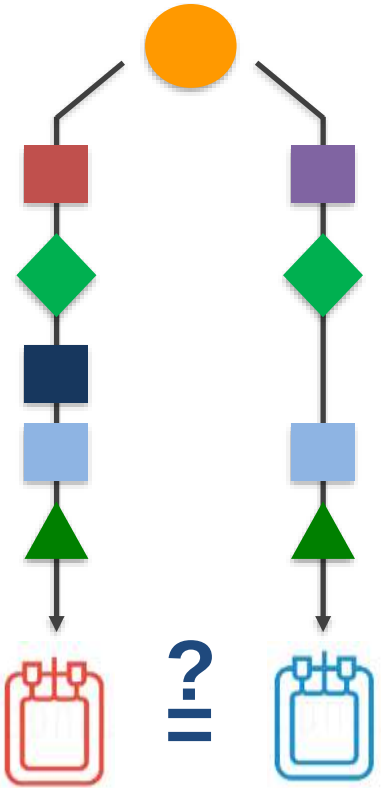
- Perform a range of characterization assays throughout development
- Evaluate multiple measures of potency
- Identify additional product attributes that reflect product performance
  - Cellular impurities (e.g., non-T cells)
  - Other process impurities
- Characterization of GE products
  - Types of edits occurring at on-target sites
  - Residual genome editing components



Product Characterization Supports Implementation of Manufacturing Changes

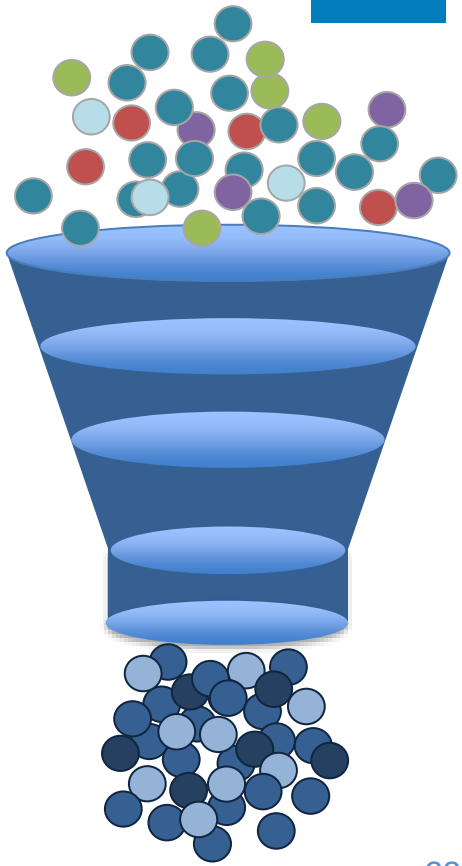
Comparability allows leveraging clinical data from pre- and post-change products

- Change in reagent, process step, scale, etc.
- Comparability assessment requirements are affected by:
  - Early vs. late stage of development
  - Minor vs. major change
  - Patient risk
- Change may be to improve an attribute or manufacturing process
  - Reduce culture time
  - Improve purity



Summary

- Appropriate materials, process design, and testing support DP quality
- Invest significant effort into understanding your product attributes during preclinical studies and early phase clinical studies
- Have a comprehensive quality and control program to maximize product quality
  - FDA Guidances, particularly the Gene Therapy CMC Guidance
  - FDA meetings, particularly INTERACT and pre-IND meetings
- Anticipate challenges so you can address them appropriately and early



Selected FDA Guidance for Industry

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), January 2020. https://www.fda.gov/media/113760/download
- Formal Meetings Between the FDA and Sponsors or Applicants, May 2009. https://www.fda.gov/media/72253/download.
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- Analytical Procedures and Methods Validation for Drugs and Biologics, July 2015 https://www.fda.gov/media/87801/download
- Drug Master Files, DRAFT Guidance, October 2019 https://www.fda.gov/media/131861/download

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- **OTAT Learn Webinar Series:**

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

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
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