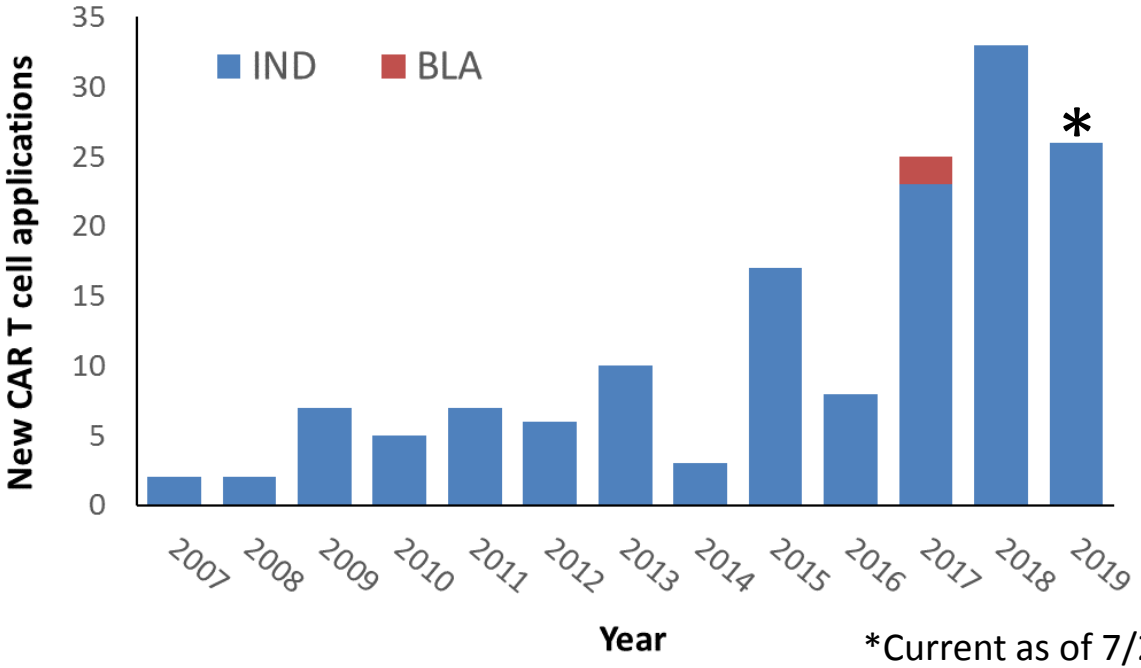
Regulatory Considerations for CAR T Cell Clinical Studies

Andrew Harmon, PhD
US Food and Drug Administration
Division of Cellular and Gene Therapies
CBER/OTAT

CAR T cell applications in OTAT

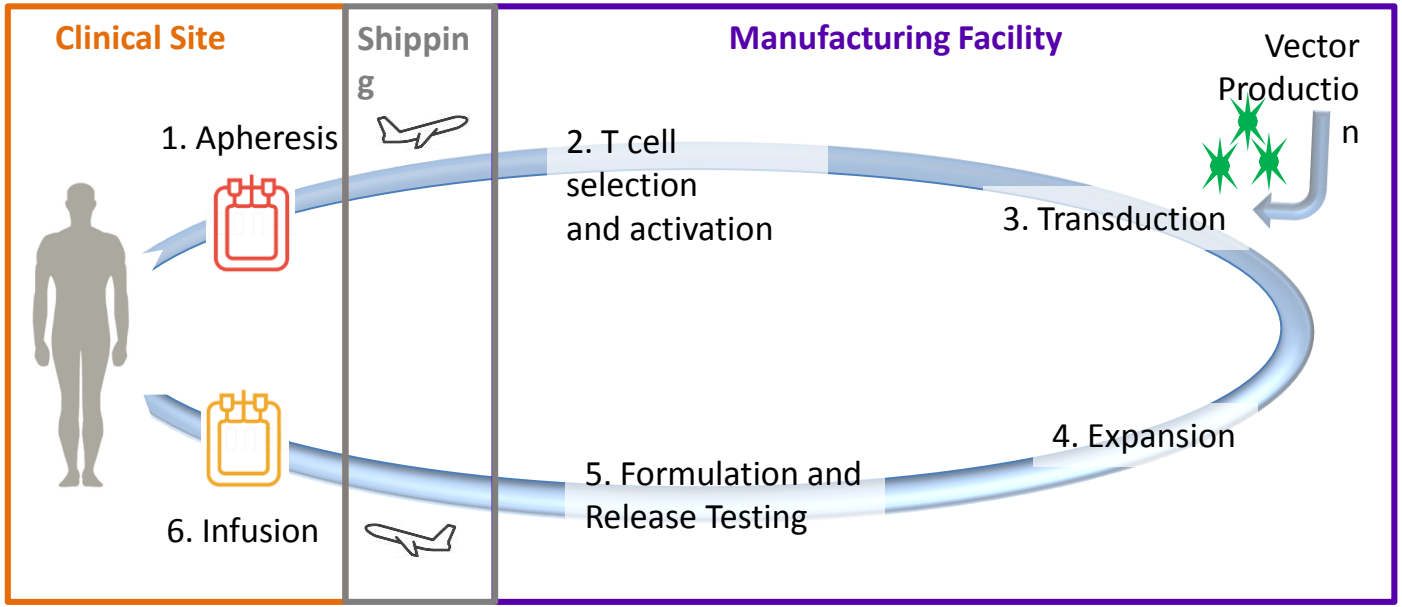


*Current as of 7/2019

- First CAR T cell IND submitted in 2001

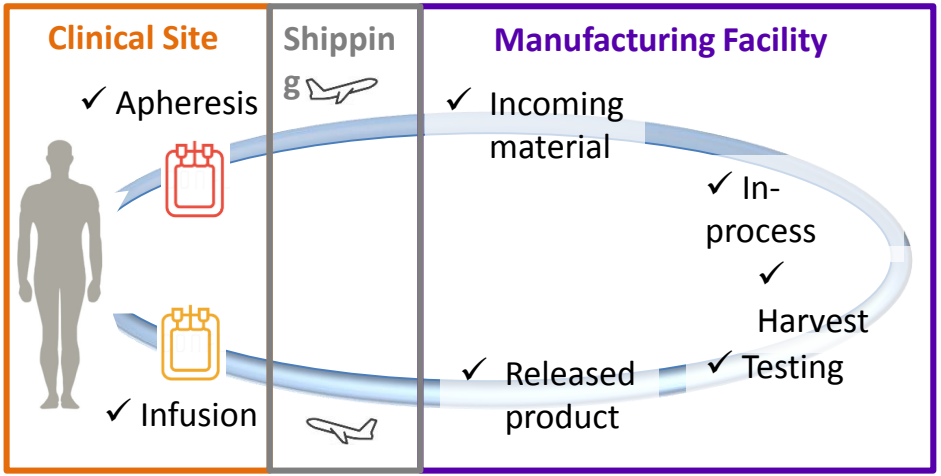
Complicated manufacturing process

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



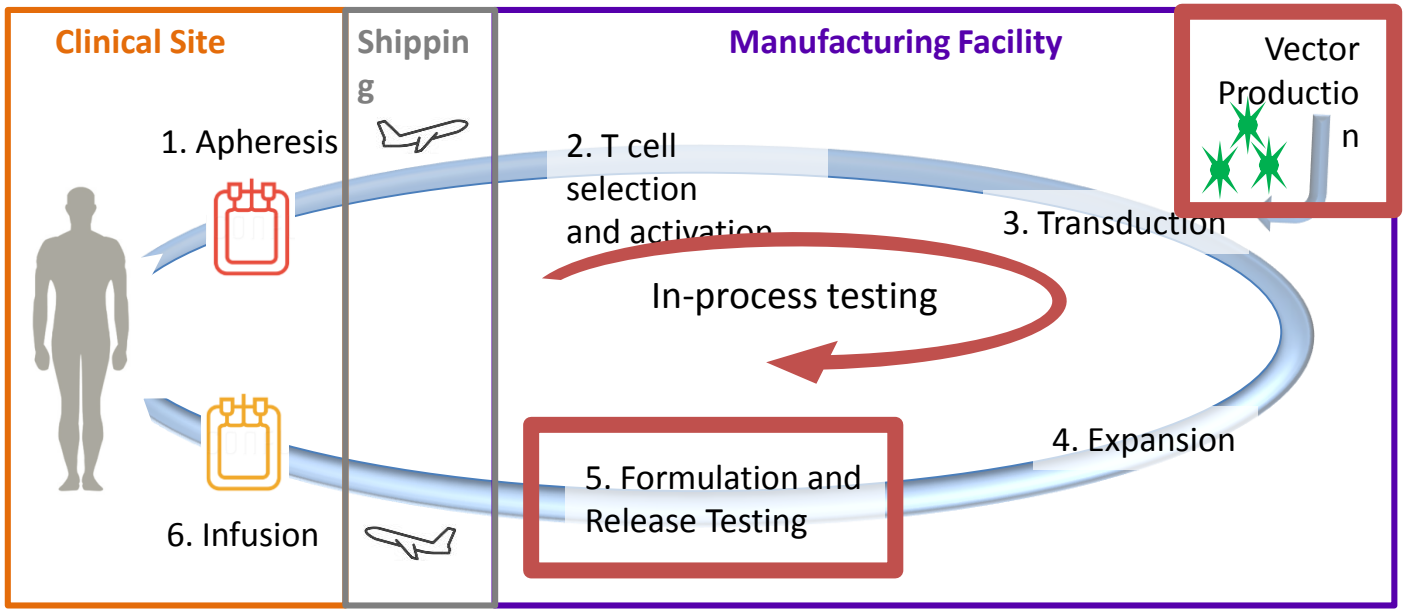
Chain of Identity

- Critical to ensure patient receives the correct product
- In place prior to start of phase 1 study
- Autologous products must be tracked from apheresis to administration
- ≥2 unique identifiers confirmed at set times by ≥2 persons
- Automated tracking systems available



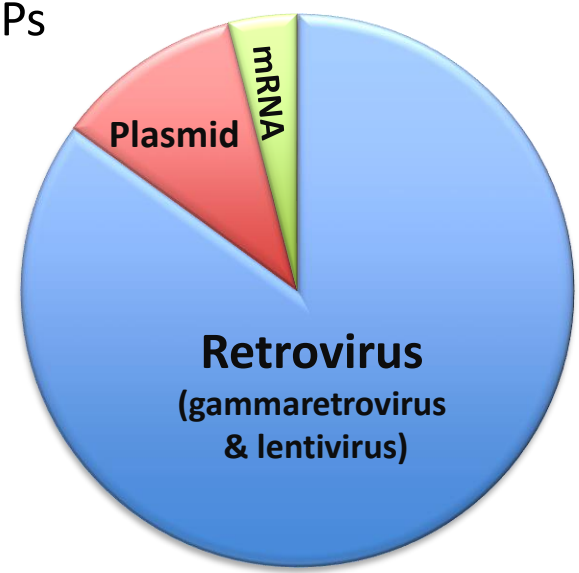
CAR T cell Testing Design

- Microbial and safety assays
- Non-compendial assays
- Managing time from production to administration



Gene Transfer Vector

- Encodes the CAR transgene
- Critical component
- Separate DS section in application
- Manufactured according to CGMPs
- Stability studies
- Subject to pre-license inspection



Gene Transfer Vector Quality

- Vector quality impacts CAR T cell quality
- Assure identity, safety, purity, and potency
- Test results prior to CAR T cell manufacturing
- Safety testing required:
  - Sterility
  - Endotoxin
  - Mycoplasma
  - *in vitro* adventitious virus
  - Replication Competent Retrovirus (RCR/RCL)

Safety Testing

	Master Cell Bank	Working Cell Bank	Gene Transfer Vector	CAR T cells
Sterility	Yes	Yes	Yes	Yes
Mycoplasma	Yes	Yes	Yes	Yes
Endotoxin	No	No	Yes	Yes
RCR	Yes*	No	Yes	Yes
In vivo adventitious virus	Yes	No	No	No
In vitro adventitious virus	Yes	Yes	Yes	No

Safety Testing

	Master Cell Bank	Working Cell Bank	Gene Transfer Vector	CAR T cells
Sterility	Yes	Yes	Yes	Yes
Mycoplasma	Yes	Yes	Yes	Yes
Endotoxin	No	No	Yes	Yes
RCR	Yes*	No	Yes	Yes
In vivo adventitious virus	Yes	No	No	No
In vitro adventitious virus	Yes	Yes	Yes	No

Safety Release Assays

- Sterility: 21 CFR 610.12
  - USP<71>: 14 days
  - Alternate methods: Culture-based, non-culture-based
- Mycoplasma: 21 CFR 610.30
  - USP<63>: 14 days
  - Alternate methods: Enzyme-based testing, qPCR tests
- Replication competent retrovirus testing: FDA Guidance
  - Biological co-culture assay: >4 weeks
  - Alternate methods for CAR T cells: qPCR, enzyme-based

  Draft Guidance for RCR testing, July 2018

Alternative Methods for Safety Testing

21 CFR 610.9 Equivalent methods and processes

"Modification of any particular test method…shall be permitted only under the following conditions:

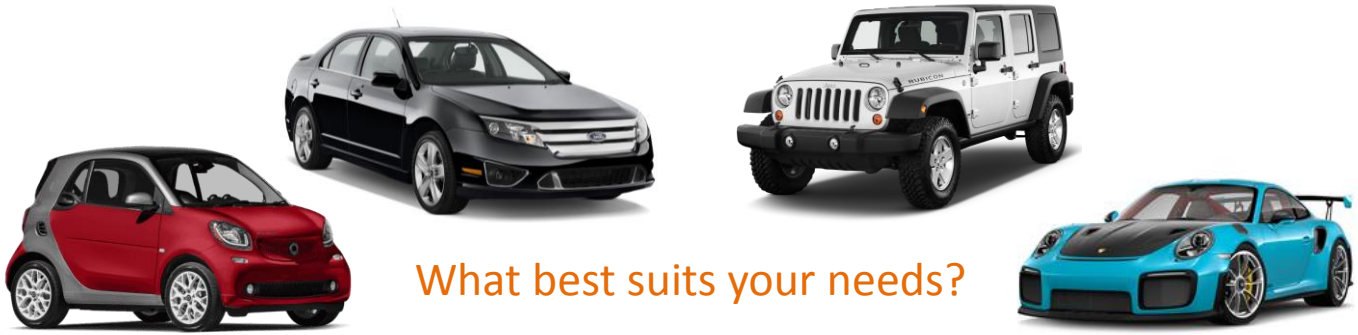
(a) The applicant presents evidence…demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the assurances provided by the method or process specified in the general standards or additional standards for the biological product"

Alternative Methods for Safety Testing

21 CFR 610.9 Equivalent methods and processes

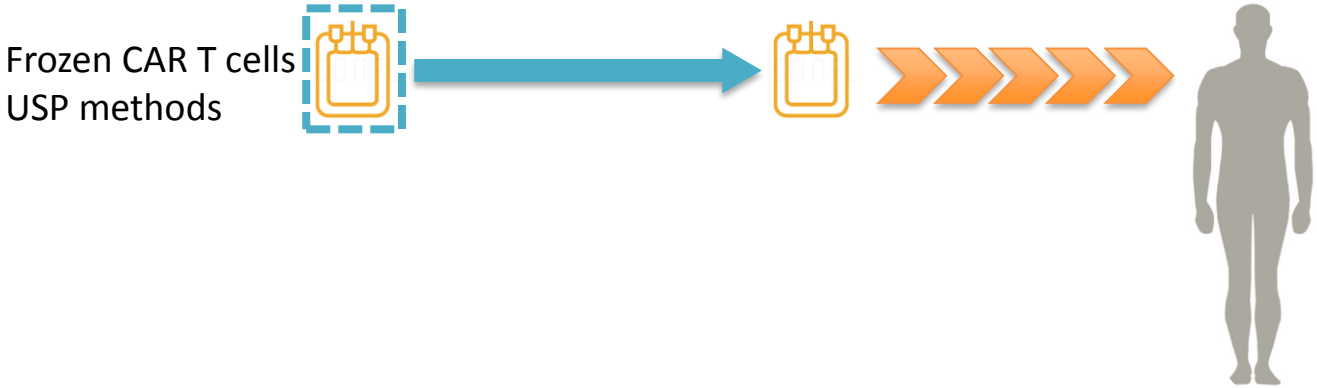
"Modification of any particular test method…shall be permitted only under the following conditions:

(a) The applicant presents evidence…demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the assurances provided by the method or process specified in the general standards or additional standards for the biological product"



What best suits your needs?

Production to infusion timeline



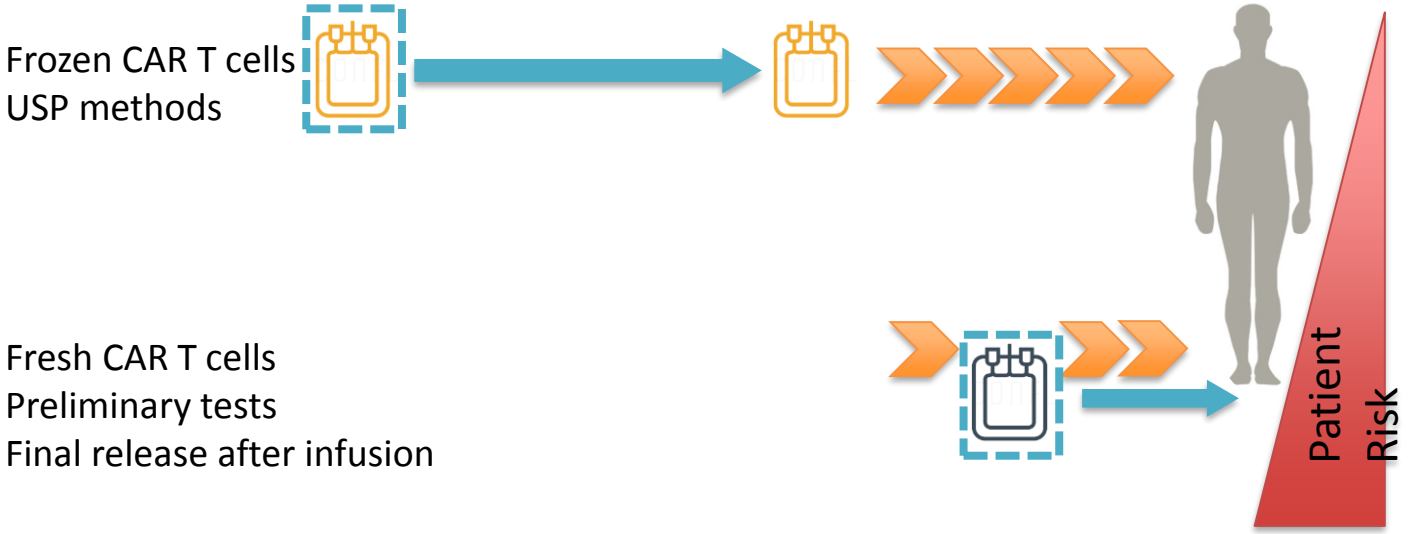
Manufacturing: 2-4 weeks

Release Testing: 2-4 weeks

Lympho-depleting Chemo

Infusion

Production to infusion timeline



Manufacturing: 2-4 weeks

Release Testing: 2-4 weeks after administration

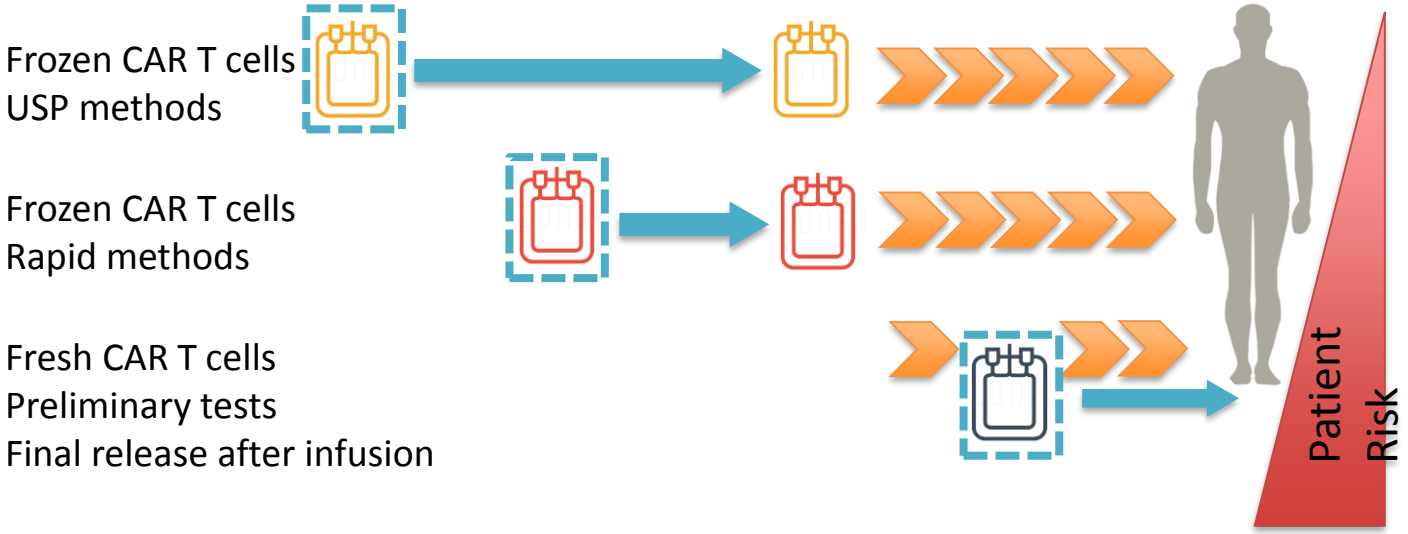
Lympho-depleting Chemo

Infusion

Expectations to infuse fresh CAR T cells

- Fresh product may provide patient benefit
  - Late stage disease
  - Rapidly progressing disease
- Fresh products may increase patient risk
  - Patients undergo chemotherapy prior to CAR T cell testing
  - Possibility of infusing contaminated lot
- Prior to administration:
  - Preliminary sterility results from in-process testing
  - Gram Stain
  - Rapid mycoplasma testing
- After Administration:
  - Final product sterility results, compendial or rapid method
  - Action plan if found to be contaminated
    - Notification and treatment plan
    - Investigation and CAPA

Production to infusion timeline



Manufacturing: 2-4 weeks

Release Testing: Rapid methods: ~1 week

Lympho-depleting Chemo

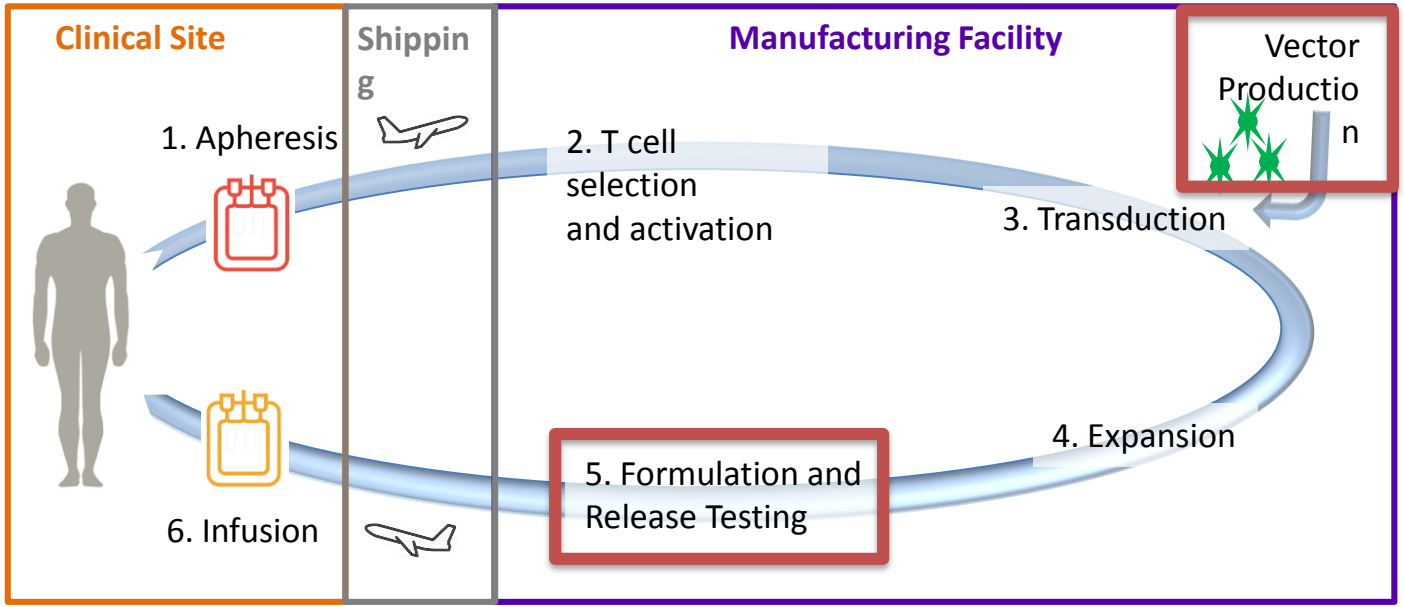
Infusion

Expectations for Rapid Sterility and Mycoplasma Tests

- IND:
  - Assay and sampling description
  - Assay verification
    - Sensitivity
    - Evidence to support wide range of species are detected
  - Bacteriostasis and fungistasis testing
    - Matrix effect i.e., antibiotics, DMSO
- Prior to licensure:
  - USP<1223> Validation of Alternative Microbiological Methods
  - Recommend discussing validation plan with FDA

Retrovirus vector-specific testing

- Replication Competent Retrovirus (RCR/RCL)

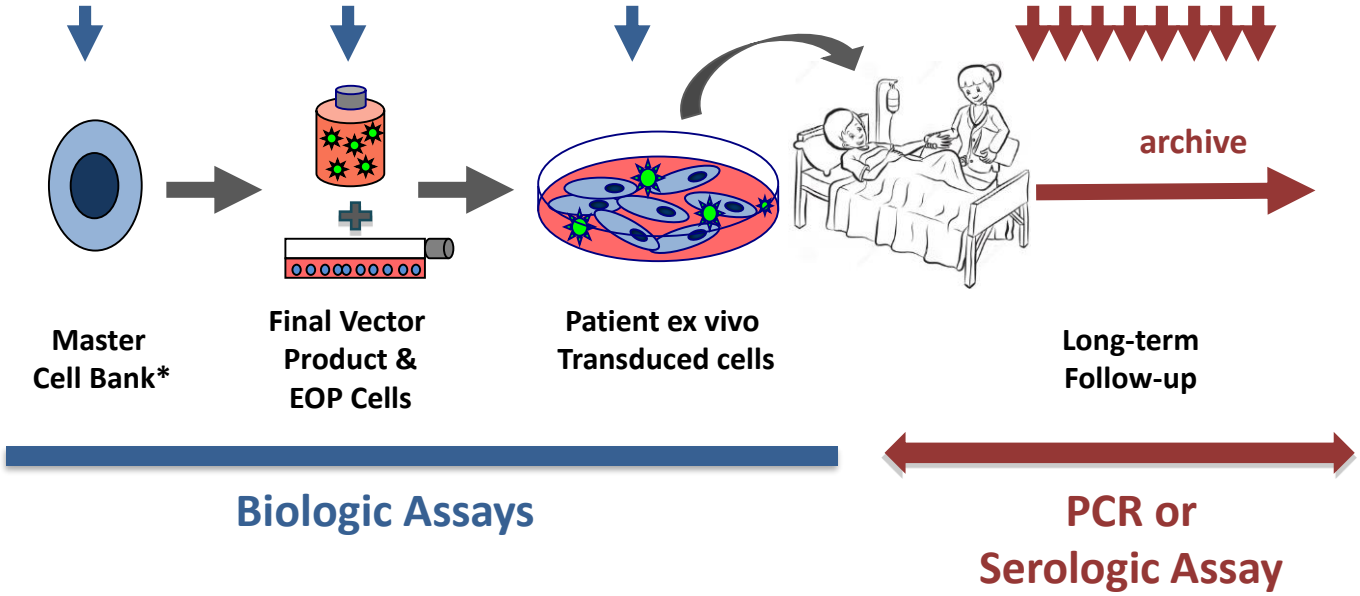


Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up (Draft, July 2018)

- Expand the scope to cover all members of retroviridae family
- Vector testing requirements updated to <1RCR/patient dose
- **Update testing recommendations for ex vivo modified cells**
- Update to patient monitoring expectations
- Add post-licensure considerations

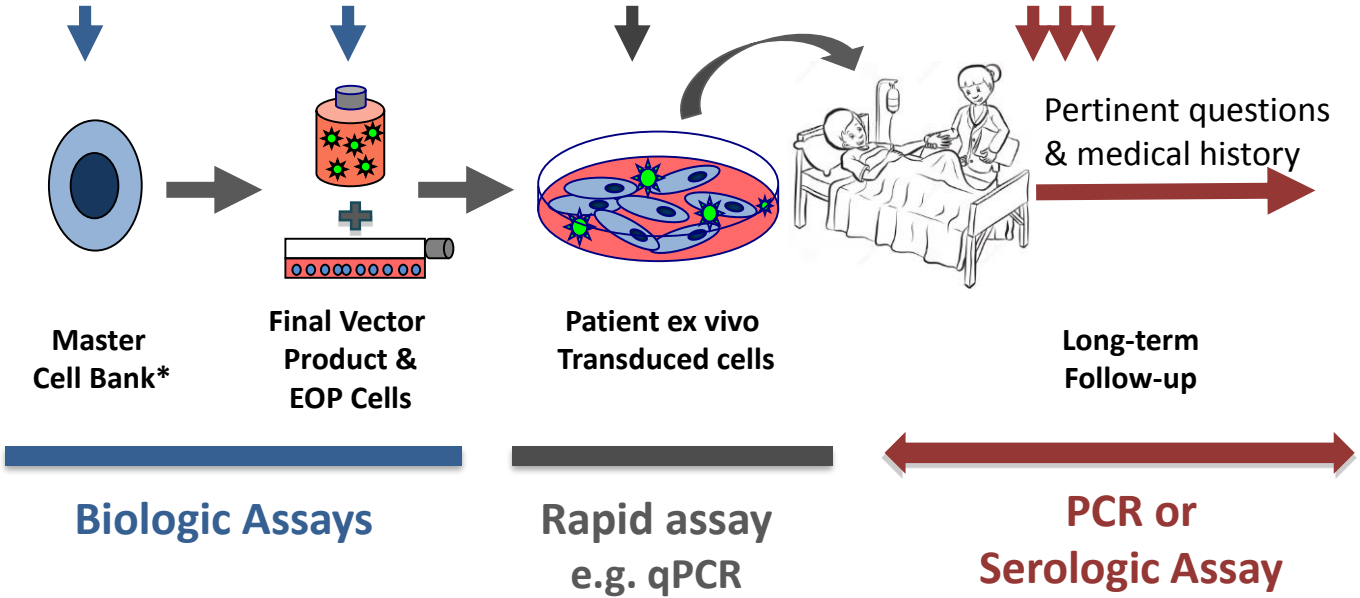
2006 RCR Guidance recommendations

- Biological testing
  - Required at multiple stages in manufacturing
  - >4 weeks to perform test



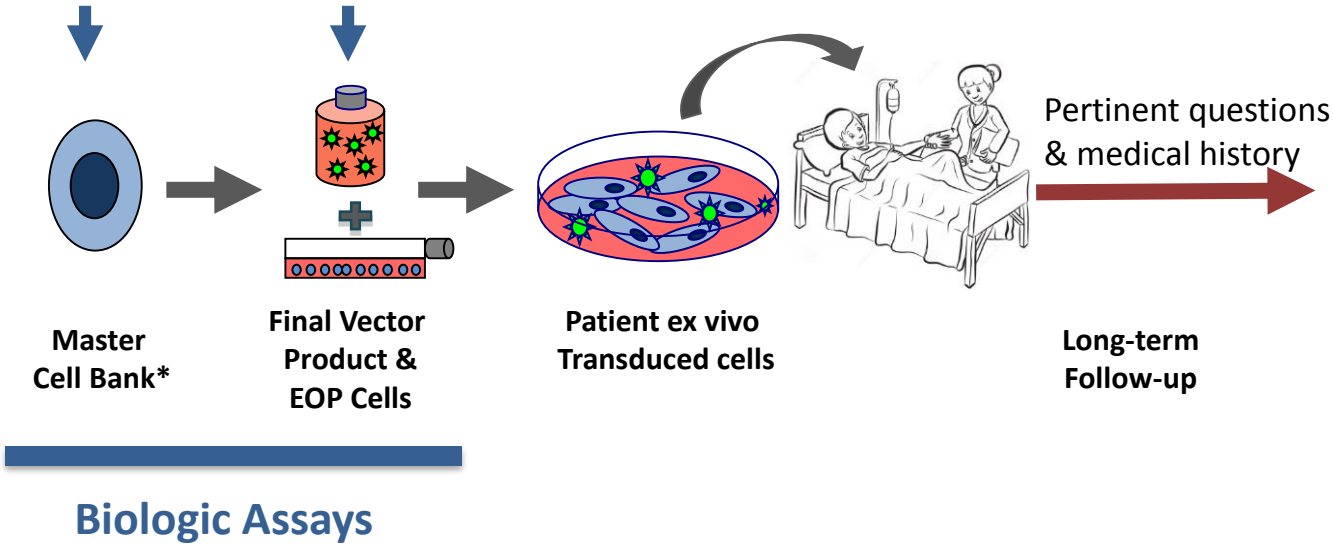
2018 DRAFT Guidance recommendations

- Biological RCR testing required for vector release
- Rapid assay for CAR T cells



2018 DRAFT Guidance recommendations

- Biological RCR testing required for vector release
- Rapid assay for CAR T cells
- RCR release testing for CAR T cells may be discontinued if justified by manufacturing experience and vector design



Information to support discontinuing the testing of ex vivo modified cells

- Discussion of safety features in the vector design
  - Split plasmid design
  - Analysis of sequence homology
  - Removal of unnecessary viral sequences
- Accumulated manufacturing experience
  - Experience with the vector; may be developmental runs
  - Experience with highly similar products
    - Justify comparison

Non-compendial Release Assays

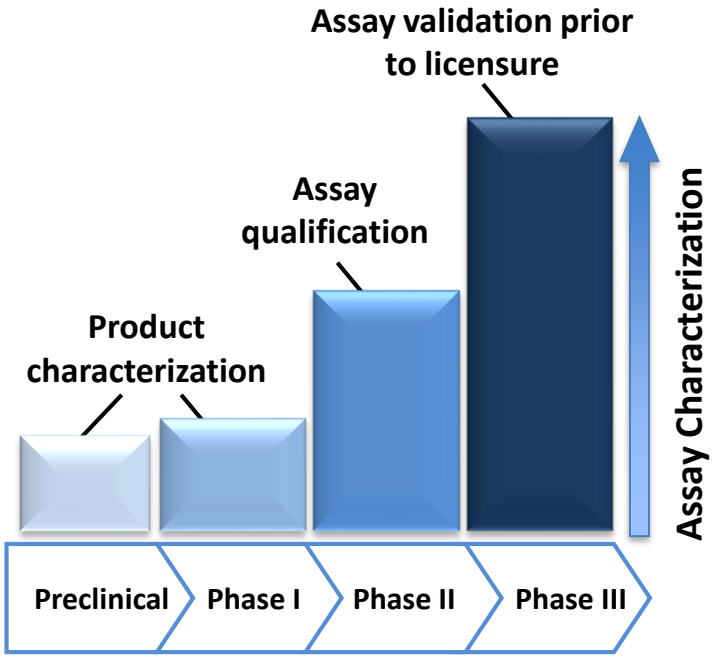
- Vector copy number
  - Safety, generally ≤5 copies/transduced cell
  - qPCR
- Cellular populations
  - Purity and potency
  - Flow cytometry
- Transduction efficiency
  - Dose and potency
  - Flow cytometry, ELISA
- Biological Activity
  - Potency
  - Cytokine release, cytolytic cell killing assay

Considerations for non-compendial assays

- No reference material, develop in house controls
- Multistep, biological assays
- Recommend using orthogonal methods during development
- Provide detailed assay description
- Acceptance criteria for licensure based on lots shown to be safe and effective

Qualification of Release Assays

- Phase 1
  - Include assay description
  - Suitable for intended purpose
  - Use of orthogonal methods
- Phase 2
  - Qualification
- Prior to Licensure
  - Validated per ICH Q2(R1)



Summary

- Monitoring and testing throughout the manufacturing process supports safe and consistent CAR T cell production
- Alternative methods for microbial assays should be qualified to support early phase studies
- Non-compendial assays should be refined throughout product development and validated for licensure

- RCR testing requirements have evolved as the field has gained knowledge and incorporated safety features into vector design

CBER Draft Guidance Documents

1. Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus during Product Manufacture and Patient Follow-up; (RCR)
2. Observing Subjects Who Received Human Gene Therapy Products for Delayed Adverse Events; (LTFU)
3. Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); (GT CMC)
4. Human Gene Therapy for Hemophilia
5. Human Gene Therapy for Retinal Disorders
6. Human Gene Therapy for Rare Diseases

https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/ucm223006.htm

Contact Information

- **Andrew Harmon, PhD**

  andrew.harmon@fda.hhs.gov

- **Regulatory Questions:**

  OTAT Main Line – 240 402 8190

  Email: OTATRPMS@fda.hhs.gov and

  Lori.Tull@fda.hhs.gov

FDA Headquarters
Federal Research Center at White Oak
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

- **OCTGT Learn Webinar Series:**

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

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.gov
- **Follow us on Twitter:** https://www.twitter.com/fdacber


FDA
U.S. FOOD & DRUG
ADMINISTRATION