CMC Considerations for the Commercial Development of CAR T Cell Products

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Introduction

This presentation will highlight some of the issues that FDA has observed in terms of product characterization and release specifications during late phase development

Topics to be discussed

- **GENERAL CONSIDERATIONS FOR PHASE 3 MANUFACTURING TOWARDS LICENSURE**

- **CONSIDERATIONS FOR MANUFACTURING HIGH-QUALITY CAR T CELL PRODUCTS**

GENERAL CONSIDERATIONS FOR PHASE 3 MANUFACTURING TOWARDS LICENSURE

Path toward Biological License Application (BLA)

- Demonstrate product is clinically safe and effective by adequate and well controlled clinical studies
- Demonstrate product is safe, pure, potent, and stable by in vitro (and/or in vivo, if necessary) methods
- Demonstrate consistency in the manufacturing process

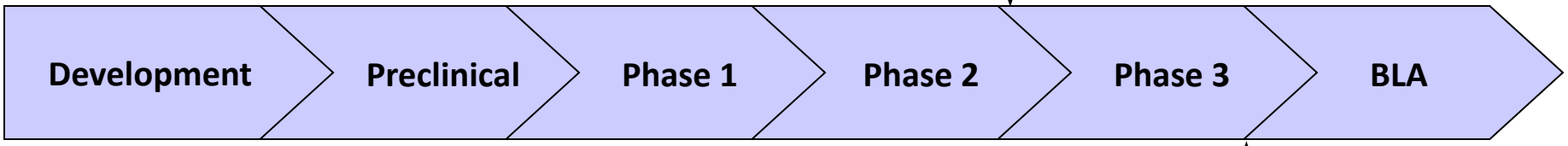
Deficiencies in product and process characterization

- Process validation
- Product- and process-related impurities
- Stability
- Potency
- Identity
- General issues with release assays
- Comparability issues
- Device considerations

Critical junctures in late-phase product development

End of phase 2

- Manufacturing process consistency
- Product stability
- Adequacy of product characterization
- Potency assay must be in place for phase III
- If product or assays are not ready, FDA may not permit phase III study
- Manufacturing changes before or during phase III may require product comparability demonstration



Pre-BLA

- Manufacturing scale-up/out or other manufacturing changes may require comparability demonstration
- Test method validation
- Facility inspection plans
- Finalizing lot release plans

CMC expectations for phase 3

Well-established manufacturing process

- Reliable process control
- Generally recommend not making major manufacturing changes during phase 3
  - If major changes are inevitable, product comparability may need to be established

Critical assays should be qualified before phase 3

- Potency – A qualified potency assay should be established by Phase 3 and must be validated for BLA
- Manufacturing experience throughout the product life cycle helps to set reasonable lot release specifications for BLA

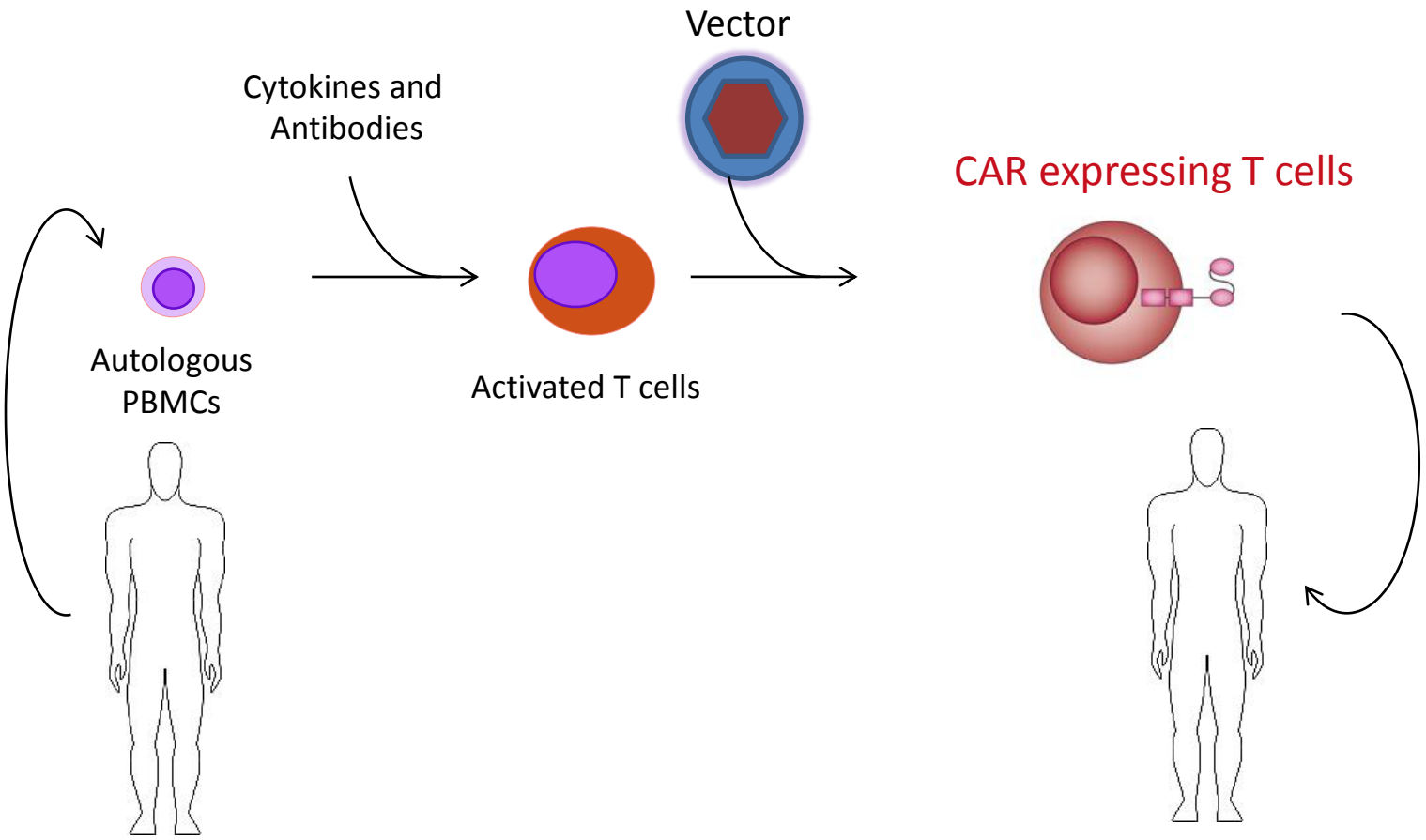
Highly advisable to meet with FDA before phase 3

End of phase 2 meeting

- Manufacturing, assays, product stability, facilities, GMPs, device development

CONSIDERATIONS FOR MANUFACTURING HIGH-QUALITY CAR T CELL PRODUCTS

Overview: Manufacturing of CAR-T cells



Considerations for manufacturing high-quality CAR-T cell products

- Product purity
- Manufacturing controls and product consistency
- Manufacturing process changes
- Product stability
- Establishing a potency assay
- Device considerations

Product purity

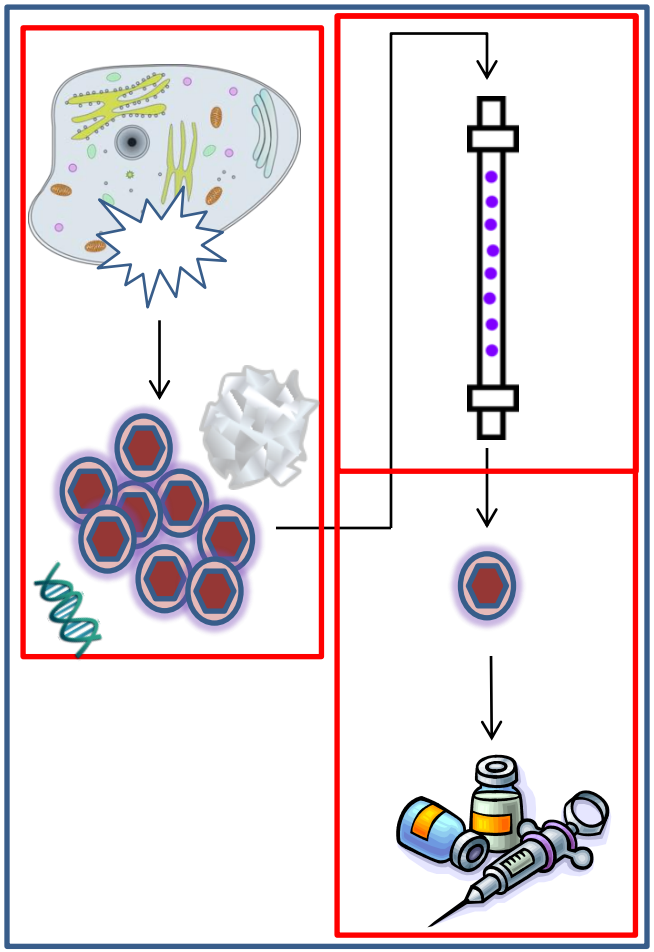
Goals for product purity (vector and cells):

- Manufacturing process should remove impurities in a reliable manner
  - Focus most on impurities that affect safety or efficacy
  - Set limits for impurities
  - Cellular products in general don't have to be completely pure but they should be well characterized

- Understand how the manufacturing process affects purity
  - How does each individual step affect purity?
  - With a good understanding of the manufacturing process, one may be able to predict how a process change will impact purity

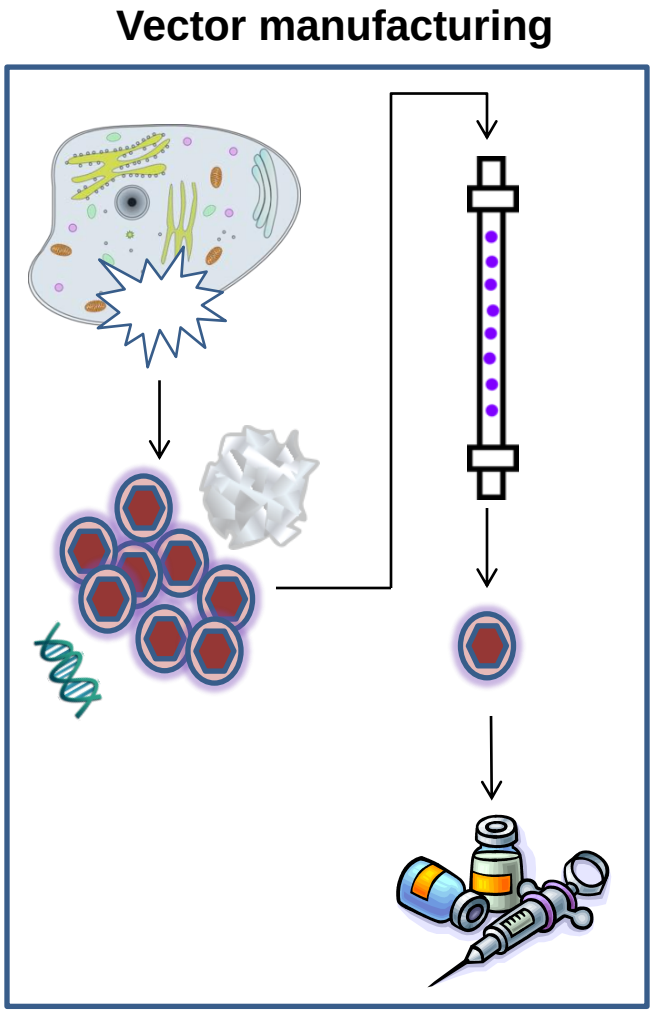
Process-related impurities

Vector manufacturing



- Media components (serum)
- Other viral vectors (multi-product facility)
- Cellular protein
- Cellular DNA
  - Use specific assay if cell has viral oncogenes
- Plasmid DNA
- Nuclease
- Chromatography resin
- Leachates
  - From tubing, bioprocess bags, filters, vials, stoppers

Product-related impurities

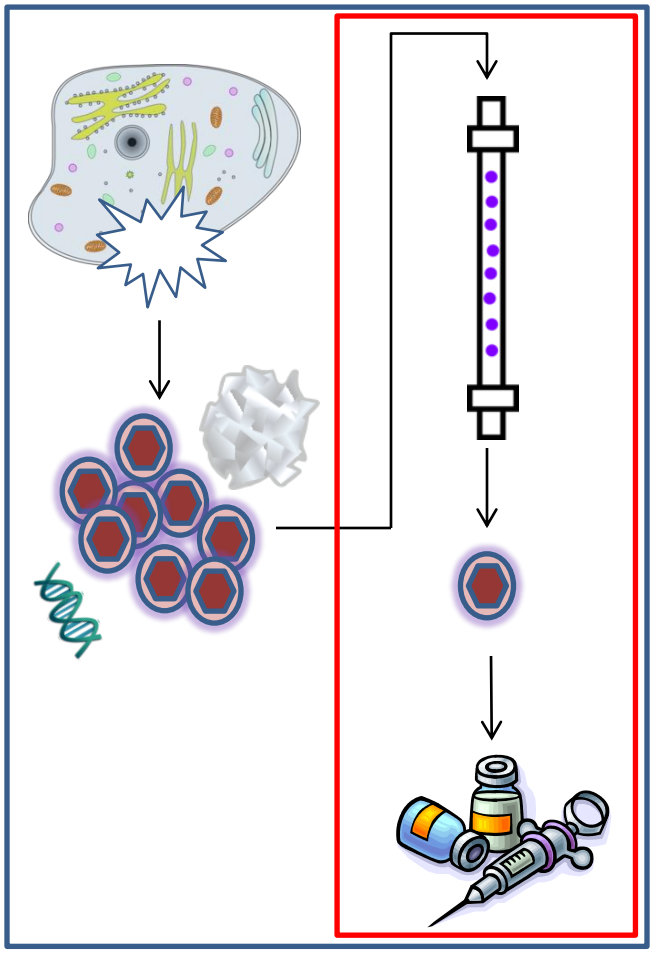


Vector aggregates

Some impurities may be harder to remove

- Non-infectious virions
- Replication-competent recombinants
- Genetic variants

Manufacturing changes can impact purity



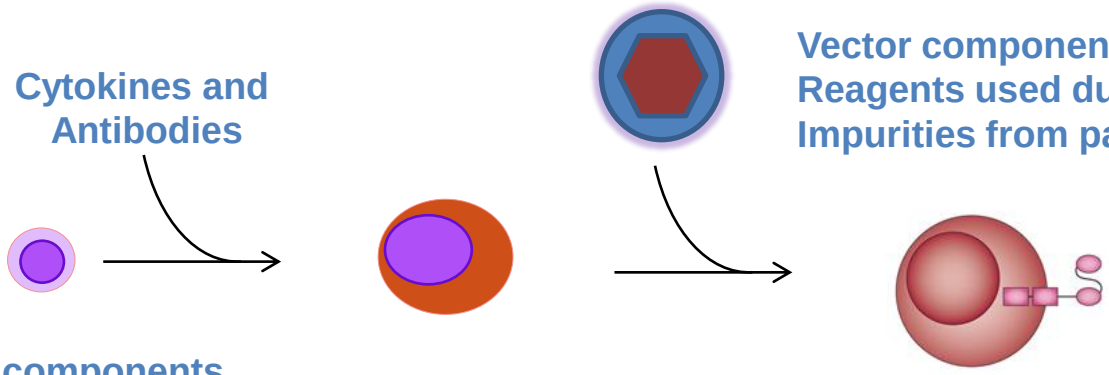
Alterations to any step of the manufacturing process may affect product purity

Changes to later manufacturing steps tend to have more impact on the final product

Even changing the type of vial might have an impact

Risks associated with specific manufacturing changes (e.g. impact on the safety and quality of the active ingredient, drug substance, drug substance intermediate, and/or drug product) should be properly assessed

Impurities in the cellular product



Considerations for manufacturing high-quality CAR T cell products

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Multi-pronged approach to product quality

- **Lot release testing**

  Final product

- **In-process testing**

  At intermediate steps during manufacturing

- **Process validation**

  Understanding how variation in the manufacturing process impacts the quality, safety and efficacy of the product

Lot Release Specifications

- Specifications:
  - Tests (e.g. analytical and biological) and acceptance criteria that confirm the quality of products and other materials used in the production of a product
- Acceptance criteria:
  - Numerical limits, ranges, or other criteria for tests described in specifications
- Incremental Approach
  - Phase 1-2: safety, acceptance limits may have wider ranges
  - Phase 3: tests more refined and acceptance criteria more defined; established limits for release assays
- BLA
  - Specifications based on validated assays and manufacturing experience
  - Include statistical analyses

Guidance: ICH Q6B (Test Procedures and Acceptance Criteria for Biotechnological/Biological Products)

Example: Lot release testing for CAR T cells

- Safety
  - RCR/RCL testing
  - Sterility, endotoxin, mycoplasma testing
  - Vector copy numbers per transduced cell
- Identity
  - Presence of CAR sequence, etc.
- Purity
  - Process and product-related impurities
- Dose
  - Number of viable T cells expressing CAR
- Potency
  - Cytokine production, tumor cell killing, etc.

Capturing process knowledge and understanding

- Qualify critical components (leukapheresis product, vector)
- Establish critical process parameters
- Validate the manufacturing process
- Monitor through in-process testing
- Meet lot release specifications
- Characterize additional product attributes

Process validation

(How you get from point A to B does matter)

Marathon Runner Busted for 'Unfair' Advantage

He was stripped of his 3rd place medal after it was discovered that after 20 miles **he got on a tour bus for 5 miles, then ran across the finish line**

(abc NEWS October 12, 2011)

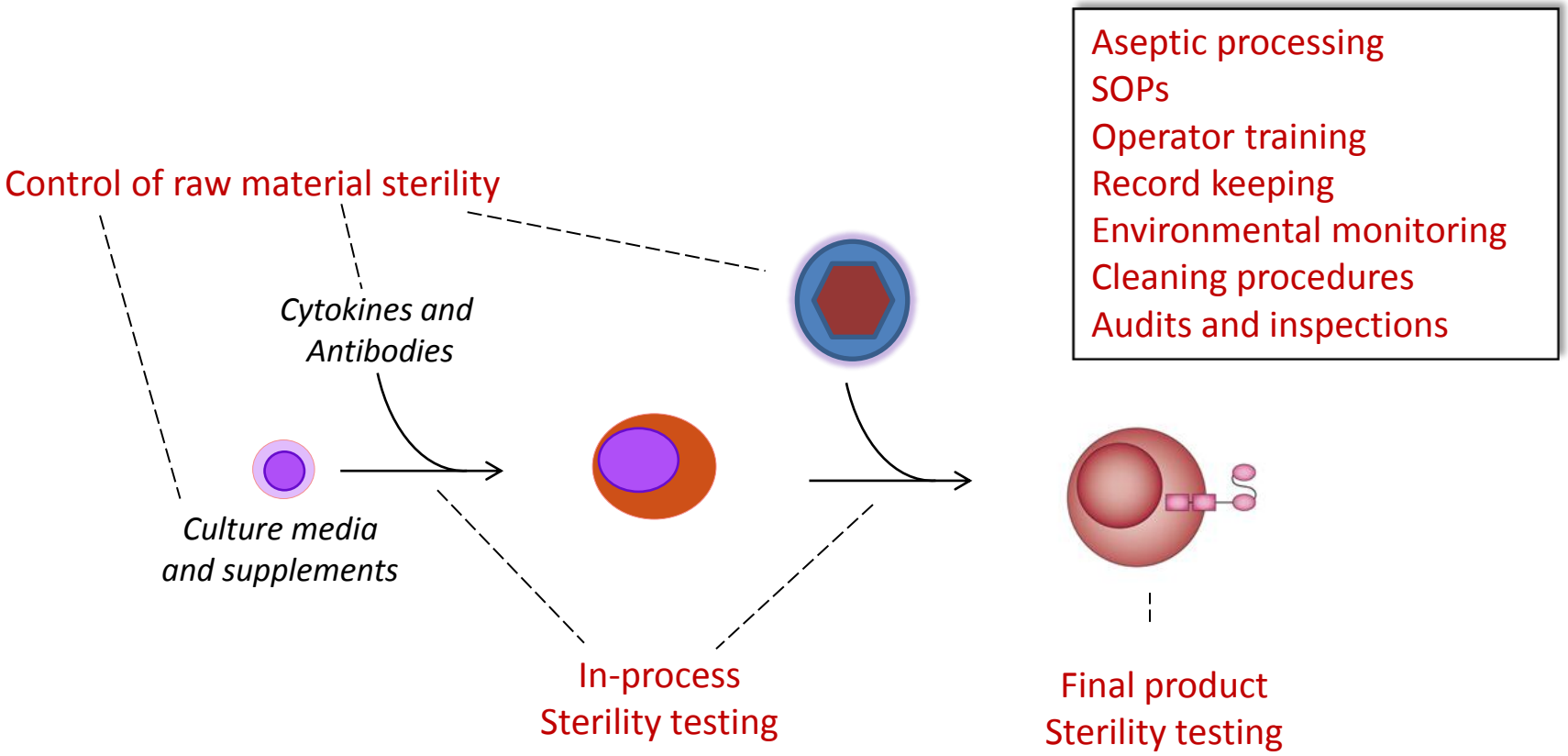
Final product testing by itself may not adequately capture all relevant information

Process validation (cont.)

- **Quality cannot be adequately assured solely by in-process and finished-product testing**
- Better to design quality, safety, and efficacy into the product
- Control each step of the manufacturing process to assure the quality of the finished product

2011 FDA Guidance: Process Validation: General Principles and Practices

Example: ensuring CAR-T cell product sterility



Control of the manufacturing process

- Understanding sources of variation
  - Reagents, donor cells, vector lots, equipment, manufacturing procedures, operators
- Understanding critical steps
  - Aseptic manipulation, transduction step, conditions for cell growth, purification steps
- Determining critical quality attributes (CQA) and critical process parameters (CPP)

Critical Quality Attributes (CQA)

- A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality
- Evaluate many attributes early during development and prune during lifecycle to those that can discern process-related changes in product safety, quality and efficacy

Critical process parameters (CPPs)

- Key variables that impact the manufacturing process
- Independent process parameters most likely to affect the quality attributes of a product
- Determined by sound science and manufacturing experience
- Controlled and monitored to ensure that the quality attributes of the product are maintained or improved

Example: CPPs for CAR-T cells

- Cell growth and expansion (growth factors, cytokines, etc.)
- Enrichment of intended T cells
- Activation conditions (antibodies, cytokines, etc.)
- Transduction conditions (multiplicity of infection, seeding density, etc.)

Contract manufacturing organizations

- **The sponsor is ultimately responsible for manufacturing, not the CMO**
- **Careful attention to the risk of cross-contamination in multi-product facilities**
  - Identity tests should distinguish your product from all other products manufactured in the facility
  - Process controls are extremely important
    - ✓ Product segregation and tracking
    - ✓ Cleaning and changeover
    - ✓ Sanitization of equipment

Considerations for manufacturing high-quality CAR-T cell products

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Manufacturing changes are sometimes unavoidable

- **Typical issues during late-phase manufacturing**
  - Scale-up
  - New manufacturing site
  - Reagents or equipment changed / discontinued
  - Test changed / discontinued

- **Change is less difficult for a well-characterized manufacturing process**

Examples of significant changes

- **Product characteristics:**

  Vector design, composition of CAR T cell subpopulations, active T cell subtypes, etc.

- **Process:**

  Transduction conditions, cell expansion conditions, manufacturing sites, cell selection method, transition from cell culture flasks to bioreactors, etc.

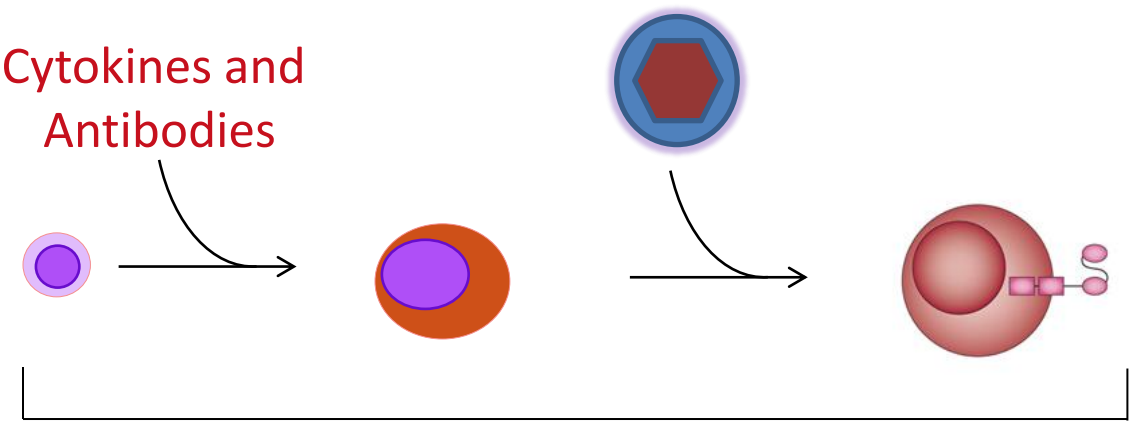
- **Materials/reagents:**

  Vector source, critical reagents (e.g., mAb, beads, cytokines, growth factors)

Supply chain vulnerabilities

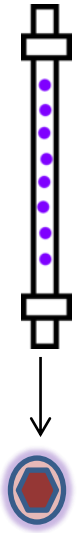
Vector from contract manufacturer

Cytokines and Antibodies



Culture media and supplements

Chromatography resin



Vials
Stoppers
Excipients

Test kits for lot release

How will changes in materials affect the final product?

Major changes require comparability testing

- **What does comparable mean?**
  - Similar quality attributes before and after manufacturing change
  - No adverse impact on product quality, safety or efficacy

- **If comparability is not demonstrated, FDA may require additional animal studies or clinical trials**

Comparability testing: Is product pre- and post-change comparable ?

Considerations

- Use robust, sensitive and relevant technologies
- Use biological and analytical assays
- Assays relevant to manufacturing change
- Side-by-side analysis of the “old” product against the “new” product
- Product consistency is important (i.e. compare multiple batches)
- Reference standards/materials should be used

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Product stability

- Need stability testing plans for the vector and the cell product
- Identify good stability-indicating assays
  - Best assays are quantitative and dose responsive
  - Measure potency
  - Accelerated stability studies may help in selecting the stability indicating assays

Product stability (cont.)

Don’t forget about:

- Stability during manufacturing holding steps
- New stability studies after major manufacturing changes
- Stability during product shipment
- For a frozen product, how long is it stable after thaw?
- Stability in delivery devices

Example: Stability programs for CAR T cells

- Apheresis materials (shipping, handling and storage)
- Vector (shipping, handling and storage)
- Final product stability studies:
  - Cryopreserved CAR T cell products
  - Fresh CAR T cell products
  - Shipping, handling and storage validation
  - Thawed product: Time between thaw and administration
- Real-time and real-condition stability studies with clinical material during product development
- Data from validated methods to support expiry dating for BLA

ICH Q5C Stability Testing of Biotechnological/Biological Products

Considerations for manufacturing high-quality CAR-T cell products

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Establishing a potency assay

- **Guided by proposed mechanism of action and in vitro and pre-clinical proof of concept data**
- **Evaluate multiple measures of product potency until you are confident you have an assay that is suitable for your needs**
  - In some cases you may wish to choose one assay for product release while continuing to collect data on other assays
  - In some cases a single measurement may not be fully informative and a matrix approach may be needed
- **Assay should be chosen based on successful qualification of the test method using your product**

Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products, January 2011

Examples of potency assays for CAR T cells

- IFN-γ production upon stimulation of CAR T cells by $CD19^+$ cells
- CAR T cell-mediated killing of $CD19^+$ cells
- Cell proliferation or other T cell activities

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Device considerations

Often the device is an after thought when it should be considered at the **earliest stages** of product development

- What is the regulatory status of the device?
- Is this the only device that can be used?
  - Combination product considerations?
- Compatibility with the final product:
  - Biocompatibility
    - ✓ Product activity after exposure to device
    - ✓ Product absorption to device
  - Cell clumping
  - Shear forces and cell viability post delivery
  - How much product is actually delivered and how much leaks back out of injection site

Summary: Preparation for late phase manufacturing

- **Product Quality**
  - Meaningful measures of quality
  - Established specifications based on prior experience
  - Comparability where relevant
- **Process Consistency**
- **Shipping, Stability, and Logistics Understood**
- **Manufacturing Strategy Determined**

Summary (cont.)

Even at the start, keep the finish line in mind

- Make good choices when designing the product and the manufacturing process
- Need especially careful planning when:
  - Making manufacturing process changes at late stages
  - Cell-based therapy is administered “fresh”
  - Manufacturing requires a reagent that is difficult to obtain
  - Product must be administered using a specific device
  - Patient eligibility relies on a specific test

Summary (cont.)

Even at the start, keep the finish line in mind

Talk to FDA about CMC at key stages during product development

- End of phase 2 meeting
- Pre-BLA meeting
- More details submitted = better FDA advice

Summary (cont.)

Even at the start, keep the finish line in mind

Talk to FDA about CMC at key stages during late-phase development

Lock down manufacturing process before phase 3

- Manufacturing changes will require comparability testing
- If changes lead to a non-comparable product or product comparability cannot be established, then new preclinical or clinical trials may be needed
- Develop assays by phase 3, validate during phase 3

Summary (cont.)

Even at the starting line, keep the long run in mind

Talk to FDA about CMC at key stages during late-phase development

Lock down manufacturing process before phase 3

Build quality into the manufacturing process

- Quality is much more than just release testing

Useful FDA Information

- References for the Regulatory Process for the Office of Cellular, Tissue, and Gene Therapies (OCTGT) http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

- OTAT Learn Webinar Series: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- Cell and Gene Therapy Guidances http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/

- Expedited Programs Guidance: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Specific guidance documents

- *Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*
- *Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications*
- *Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events*
- *Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors*
- *Potency Tests for Cellular and Gene Therapy Products*
- *Process Validation: General Principles and Practices*
- *Analytical Procedures and Methods Validation for Drugs and Biologics*

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- **OTAT Learn Webinar Series:**

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