

Early Stage CMC considerations for Source Materials and Manufacturing in Cellular Therapy

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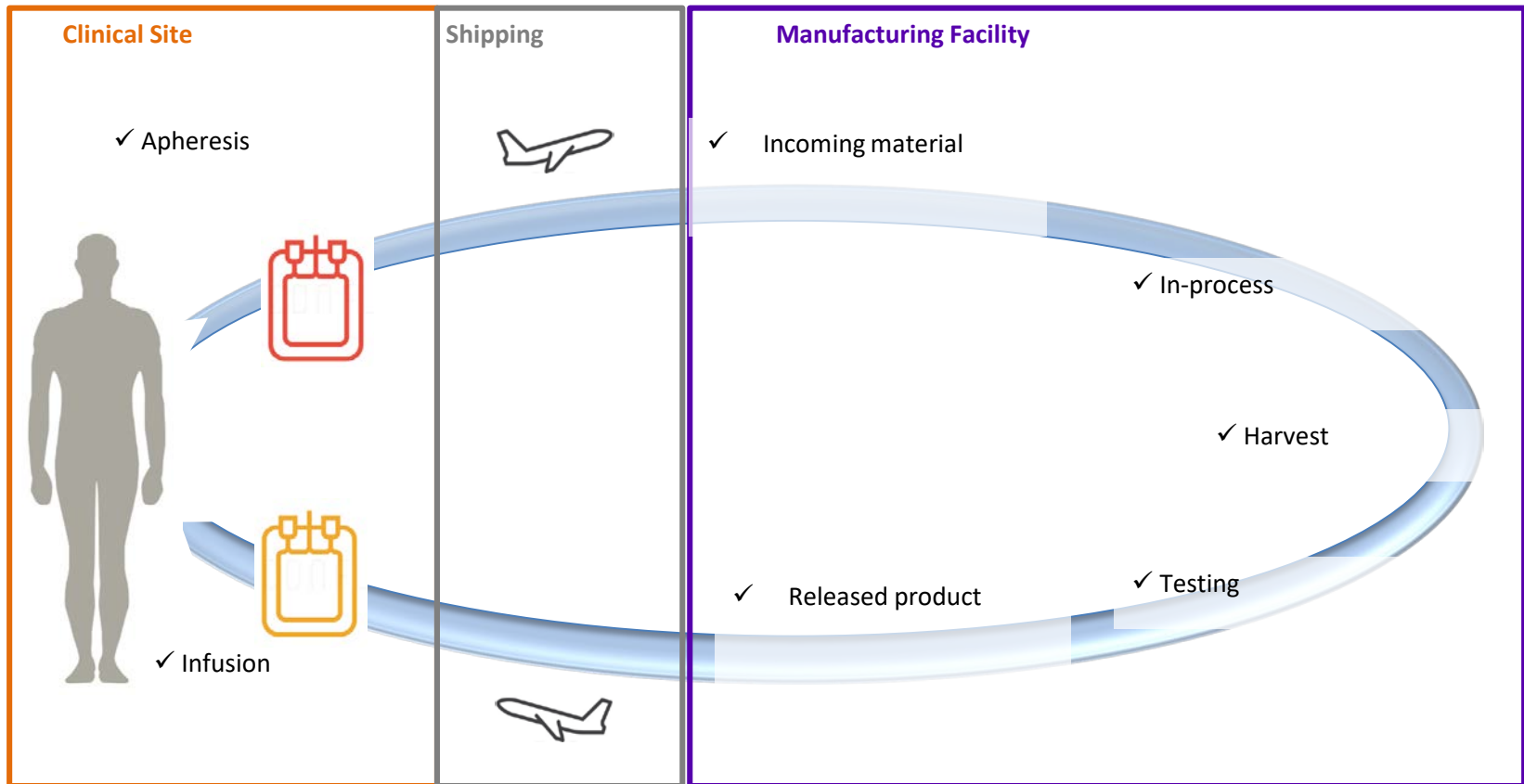
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Topics

- Early stage considerations for Source Materials:
Autologous and Allogeneic
 - Chain of identity
 - Collection
 - Handling
 - Container closure
 - Shipping
 - Shelf-life
- Early stage considerations in Manufacturing:
 - Critical Quality Attributes (CQA) and Lot Release Specifications
 - Considerations for changing the process or specifications in manufacturing
 - cGMP considerations

Maintaining Chain of Identity

- Assure identity is maintained from source material collection through in-process manipulations, testing, therapy delivery, and product administration.



Autologous Source Materials



- Donor Eligibility determination is not required.
 - Cells for Autologous use must be labeled:
 - FOR AUTOLOGOUS USE ONLY” (21 CFR Part 1271.90 (b)(1)), and “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” if donor testing and screening is not performed (21 CFR Part 1271.90 (b)(2))
- Determine if manufacturing procedure increases the risk of propagation of pathogenic agents that may be present in the donor; take appropriate action if needed
- Take precautions to prevent the spread of adventitious agents to persons other than the autologous recipient

Allogeneic Source Materials

- Donor Eligibility Determination is required.

Donor Testing:

- Conduct required testing - both antibody and nucleic acid methods (as applicable)
- Use of CLIA certified lab (or CMS equivalent)
- FDA-licensed, approved, or cleared donor screening tests
- Timing of specimen collection
- Testing performed on donor's mother if donor is one month or less

Donor Screening:

- Appropriate risk factors, clinical evidence, and physical evidence acquired
 - Questionnaire includes information on Zika virus
- Pooling of cells from multiple donors is not permitted
21 CFR 1271.220 (b)

Source Materials Collection



- Source Material collection variability:
 - Patient-to-patient differences
 - Different equipment and SOPs used at different collection centers
 - Experience of collection center personnel
- Aseptic steps should be used to prevent contamination
- Segregation: Consider using dedicated equipment, single use supplies, dedicated rooms, segregated by time
- Labeling and Tracking: Use labels with at least 2 unique identifiers, bar coding, points of verification, etc. to maintain identity and track donor through all steps

Handling Apheresis Materials: Fresh and Frozen



- Collection center (local vs. long distance): establish conditions for transport and written procedures to define storage conditions
- Transport of materials may have logistical constraints- Timing, limitations on scheduling
- Aseptic process steps should be used for cryopreservation
- Consistency across different collection centers should be maintained – freezing media, methods
- Suitability and acceptable quality for further manufacturing - yield, recovery, cell number, dead cells, composition, etc.

Source Material Containers/ Container Closure



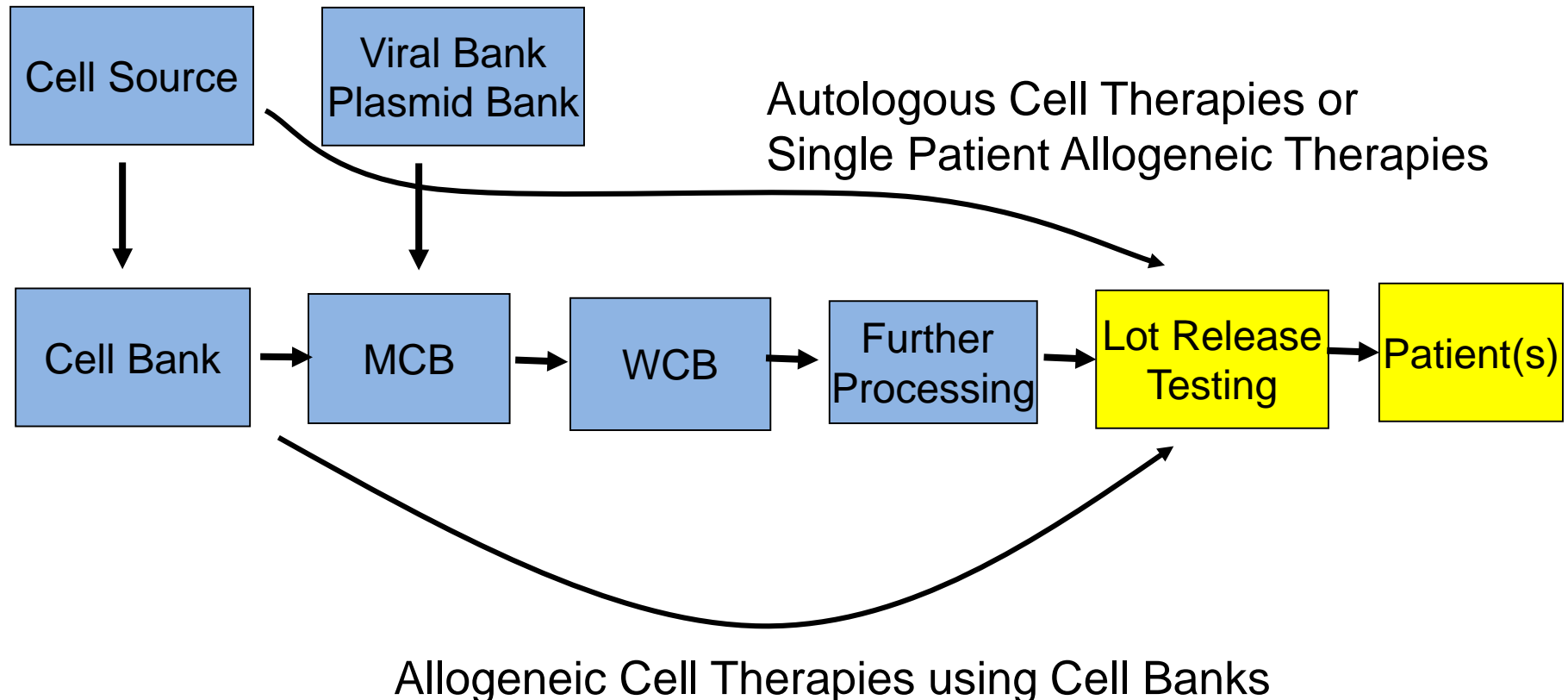
- Recommend use of approved or cleared bags; If cryovials are used, use highest quality possible
- Visual inspection of product in container: Examine for signs of leakage, appropriate color, clarity, clumps, foreign material
- Materials (serum, etc.) added by apheresis centers should be qualified
- Supporting documentation/procedures: qualify materials and procedures as necessary
- Sponsor is ultimately responsible for ensuring safety and quality of the source material

Shipping considerations

- How will responsibilities and tasks be divided up between collection center and manufacturing site, and what oversight will sponsor provide?
- Shipping qualification:
 - Qualify shipping container
 - Use temperature data loggers
- Shipping logistics:
 - Should evaluate stability of source material under worst case scenario and establish shelf life
 - Plan shipping routes and times to fit within shelf life
 - How will you handle delays in shipping?

Cell Banking systems

- Cell banks may provide source cells for downstream manufacturing (e.g., *ex vivo* expansion, differentiation, activation) of cellular products (or sometimes cell banks can also be the final product).





Considerations for Cell-bank based products

- Cell banking provides a mechanism for the consolidated storage of expanded cells identified to be characteristically the same or substantially similar that contributes to the consistency in the production of final product lots.
- Cell banking permits comprehensive testing for more extensive product characterization.
- Unlike immortalized cell lines, most cell bank based cell therapies are limited in passage number and scale. So developers should design their process to meet the required scale, understand the limits of the bank, and plan for when and how it will be replaced.

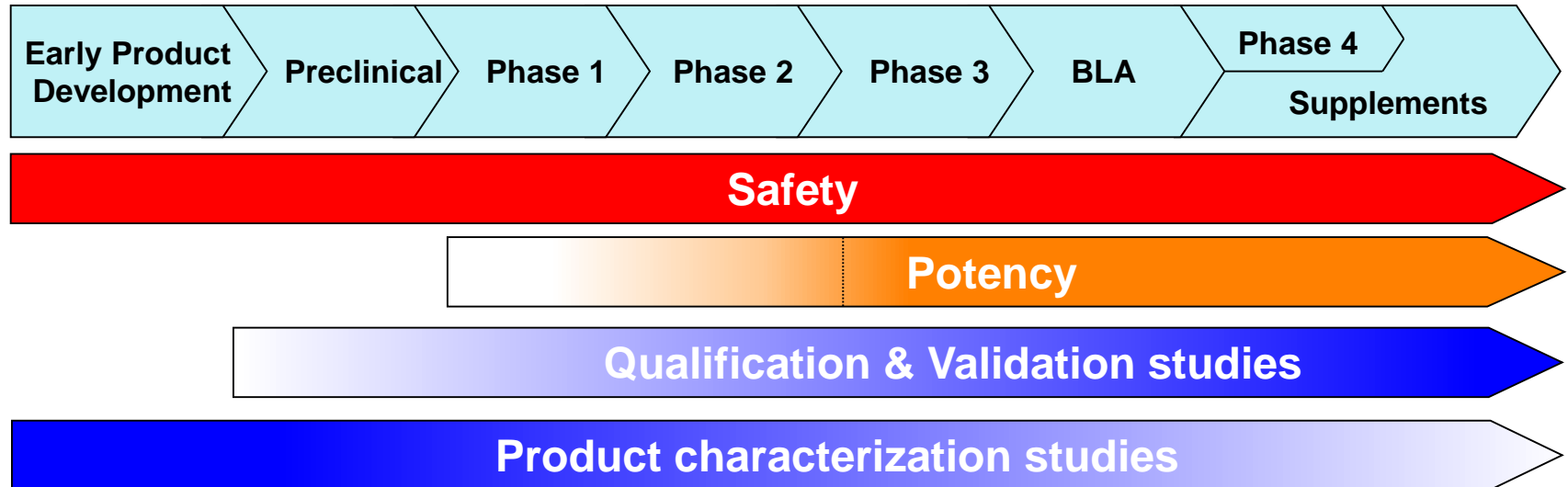
Cell Bank Testing

- Cell bank safety testing is important as higher risk is associated with the higher number of doses to treat a larger number of patients.
- **Safety Testing**
 - Sterility, mycoplasma, endotoxin
 - Human relevant communicable disease agents testing
 - Adventitious virus testing – in vivo and in vitro
 - Retroviral testing when applicable
- **Potential cell characterization tests**
 - Cell viability- doubling time
 - Genetic stability- cytogenetic analysis
 - Identity testing- genetic fingerprinting
 - Biological assays
 - Cellular composition and heterogeneity

Early Stage Manufacturing Considerations

Product stages and CMC review concerns

The stage of product development guides the review concerns, with safety being the primary concern at all stages



- Product characterization occurs throughout the lifecycle, but critical details should be determined early
- Most qualification studies are required for Phase 1 to ensure safety, but some qualification/validation studies do not occur until late in the lifecycle
- Some properties (e.g. stability, purity, identity, etc.) overlap both safety and potency

For Phase 1 the emphasis is on safety

- Preclinical animal studies should have been conducted using product **manufactured like the clinic lot under an IND**
- Safety should be designed in the product. Safety considerations for **source material, reagents, vector, gene editing, etc.**
- **Safety testing** (sterility, endotoxin, mycoplasma, identity and purity, etc.)
- Some *in vitro* proof of concept data should exist (especially for pediatric products)
- Demonstrate the **ability to manufacture** the product
- **Establish specifications** to ensure minimum quality
- Should have **preliminary shipping and stability data**



Key Features of a Rigorous and Robust Cell Product Manufacturing Process



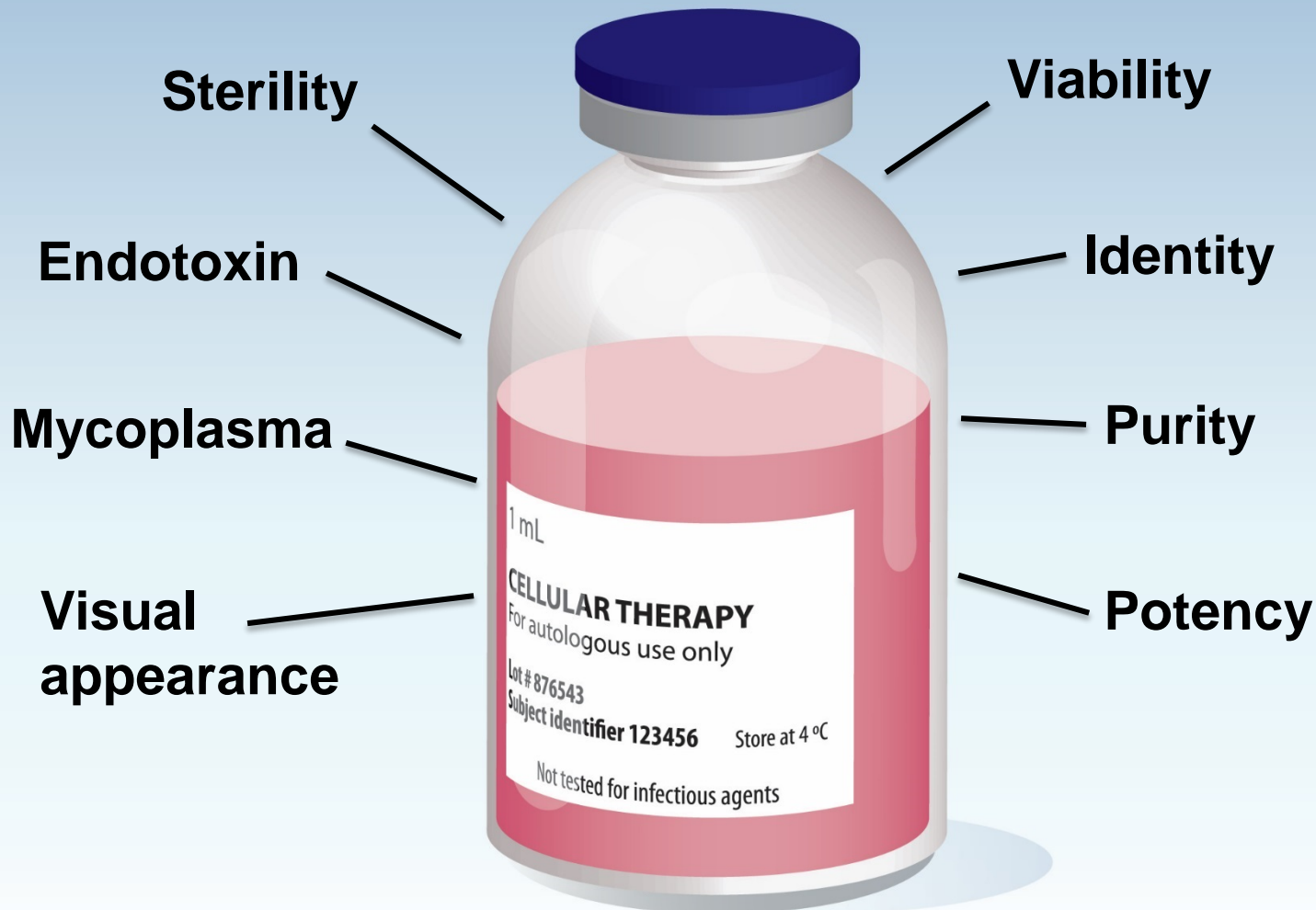
Demonstrated capability to consistently manufacture a cellular product by establishing:

- ➔ A well-controlled manufacturing process that relies on practices and procedures executed according to standardized written procedures.
- ➔ Rigorous qualification program for source materials, reagents, ingredients, excipients and components used throughout the manufacturing process.
- ➔ In-process and final product release testing demonstrating overall product quality and safety/sterility.
- ➔ Identification of Critical Quality Attributes (CQAs) representing physical, chemical, biological or molecular properties or characteristics useful for determining product quality.

Lot release specifications exist to set expectations for product safety and quality



Lots that don't meet these cut-offs should not be distributed and used



Common issues with choosing product release specifications



- Specifications not capturing key product attributes (critical quality attributes)
- Criteria inconsistent with manufacturing experience
- Lack of supportive data or rationale
- Only measuring what you want and not what you don't want
- Criteria set for a very wide range
 - could add variability to clinical trial
 - May make it more difficult to qualify assays and processes
- Misinterpretation or over-interpretation of data

CQA, CPP, and specifications are not meant to be static- they should be continually evaluated/ revised as needed

- Additional product characterization data may indicate a better way of ensuring quality
- Clinical outcome data may provide clues as to what product properties are the most important
- Additional manufacturing experience may guide CQA and Critical Process Parameters (CPP; the process that is designed to achieve CQA)



Carved in stone



Continually improving

- Changes to CQA could include either revising existing criteria, or adding or removing a specification (as supported by product characterization data)
- But since these have tremendous impact, revise cautiously!

It is easier to accommodate manufacturing changes at earlier developmental stages

- Product knowledge should increase with stage of development (identity, purity, stability, potency, relevant characteristics, biological function, etc.). Increased knowledge allows for better risk assessment.
- Consider manufacturing changes that might be needed to accommodate larger trials and commercial production.
- Manufacturing changes can be implemented at any stage, but the potential impact of a manufacturing change can increase the farther you are along in the product lifecycle.



Phase 1 and 2 may be a good time to implement a major manufacturing change prior to conducting phase 3 studies. However, often these phases are on autopilot.

A little planning up front can help avoid problems later



Think in advance about:

- Donor eligibility of source material
- Cell bank qualification
- Cell bank capacity
- Logistical issues for products with short shelf lives
- Scale up needs
- Second source for custom or critical materials
- Qualification & validation

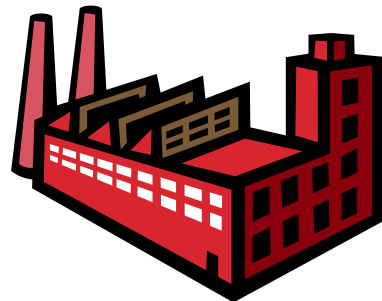
Situations where additional product characterization and analysis may be needed



- Process qualification and validation studies (to demonstrate manufacturing consistency)
 - Additional in-process and final product attributes, yield
- Comparability studies after a major manufacturing change (e.g. new process step, new facility, new critical reagent, etc.)
 - Additional measures of identity, potency, purity, etc.
 - Yield
- Stability studies (assessment of product attributes that are stability indicating should be performed)
 - Genetic stability and identity of cell lines
 - Evaluate apoptosis in addition to viability
 - Additional measures of potency

GMP considerations

- GMP manufacturing is not required for phase 1, but they are still expected to *control manufacturing*
- There is more than one way to be GMP compliant
- No two GMP facilities will be exactly alike- facility design is dictated by the products being manufactured
- GMP may “*improve*” the product, but mostly it allows you to *control* product quality and safety, and to help ensure manufacturing consistency
- GMP cannot prevent all manufacturing errors from happening, but can help ensure that controls are in place to catch them and take appropriate corrective actions



Summary

- Some considerations are common to all source materials, whereas others are more unique to certain types of source materials (e.g. donor eligibility testing and screening is required for allogeneic donors)
- Consistency is needed between clinical protocol and CMC section in describing how source material will be collected, handled, and shipped
- Need to track cell product lots through chain-of-identity system
- Characterization of cell-based products is needed to ensure product safety and consistency
- CQA, CPP, and specifications should be continually evaluated and revised as needed during product development
- Manufacturing changes are inevitable, but they are easier to accommodate early in product development, so plan ahead

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