Commercial Process Control Strategy Considerations for Cell Therapy Products

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Introduction

Cell therapy products, in general, follow an accelerated clinical development pathway

- No requirement for large animal model testing with representative clinical material – shortened FIH timelines

Regulatory expectations for the development of cell and gene therapy products are continuing to evolve

- A risk-based approach considering product, process and facility knowledge will need to be used to develop a robust control strategy

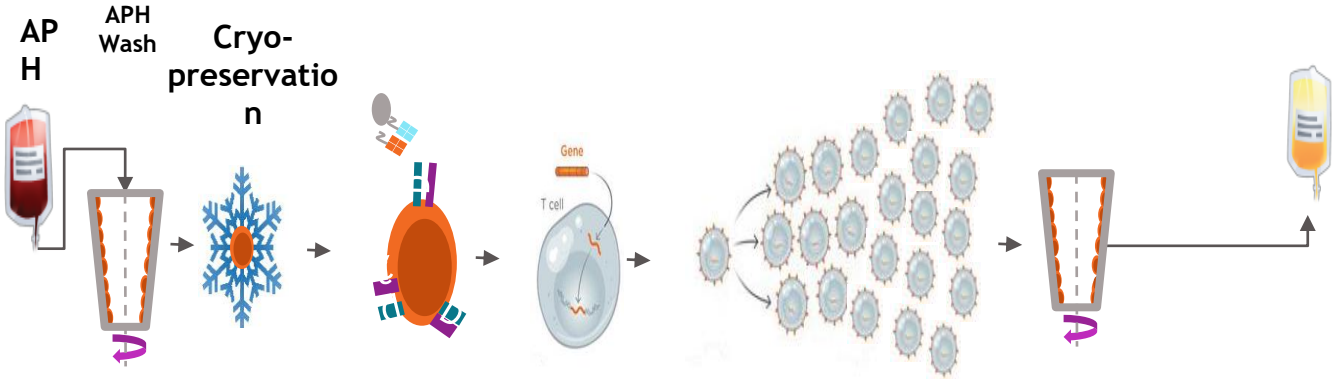
Control strategy should include:

- Process Parameter Controls
- Control of raw materials, excipients and consumables
- Procedural Controls
- Testing Controls
- Process Monitoring

Control strategy development for an accelerated autologous cell therapy product is discussed

Autologous Cell Therapy Manufacturing Process

PBMC Isolation	Activation	Transduction	Expansion	Harvest/Wash/Formulation



Aph- Cryo	Thaw - Transduction	Expansion - Product

Key Elements of Control Strategy

Process Parameter Controls

Raw Materials

- Apheresis Materials
- Components and Consumables
- **Vector (Separate process and analytical control strategy will need to be defined for its manufacture)**
- Excipients

Procedural Controls

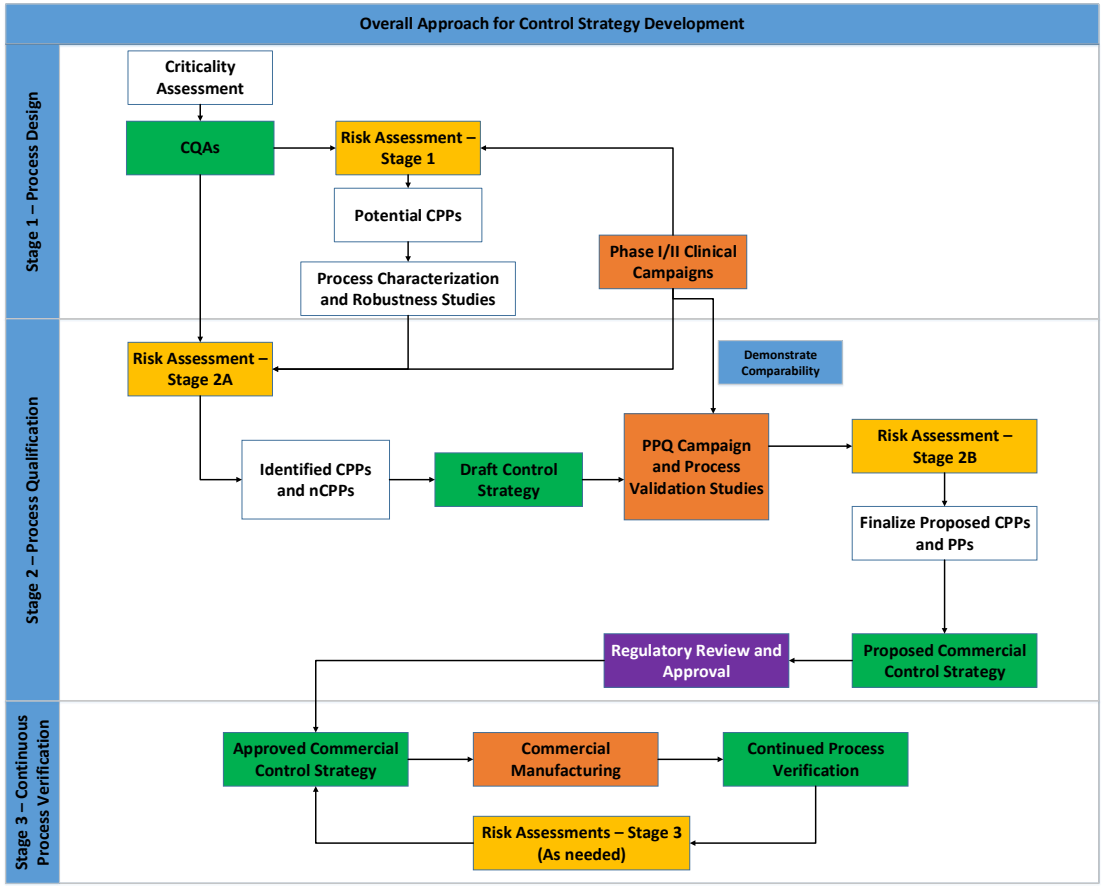
- Aseptic Manual Processing
- Facilities and Equipment
- Environmental Monitoring
- Personnel training

Testing Controls

- Release Specifications
- In-process Testing
- Stability
- Extended Characterization

Continued Process Verification

Overall Approach for Control Strategy Development



Stage 1 – Process Design

Critical Quality Attributes (CQA) Assessment

CQAs include two categories

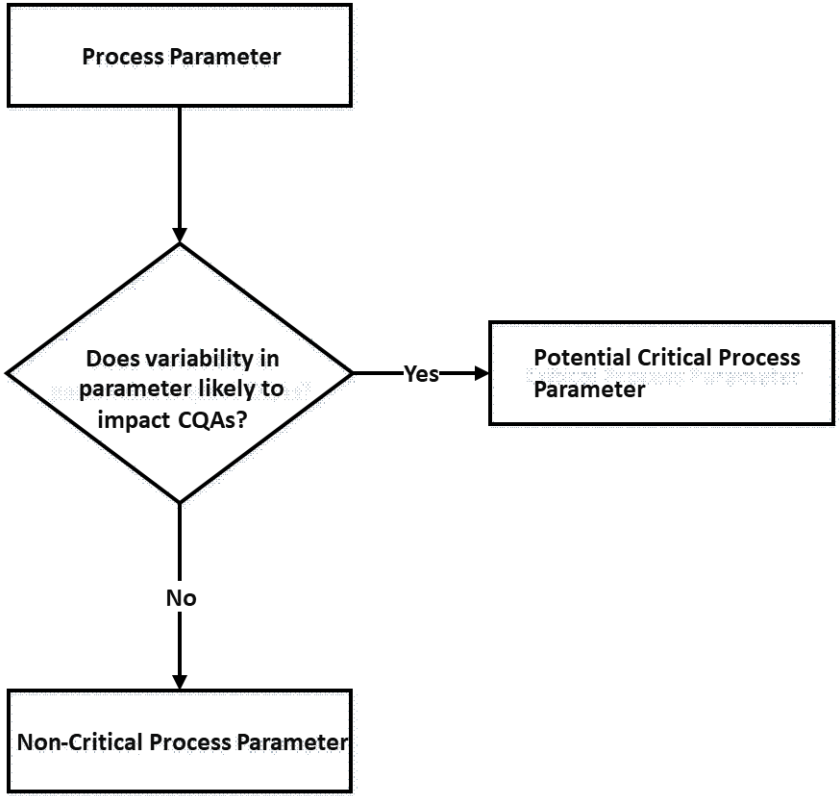
- Obligatory CQAs
  - Quality attributes that do not require risk assessment for identification because of the known impact to product quality, efficacy, and safety or are required by ICH guidelines.
  - e.g., Sterility, Endotoxin, Mycoplasma
- Risk Based CQAs
  - Quality attributes of DP that need to be assessed through a risk and knowledge-based approach.
- Identified CQAs were used in the risk assessment of Process Parameters

- Example list of CQAs

Category	Attribute
Safety	Sterility
	Mycoplasma
	Endotoxin
	Replication Competent Lentivirus (RCL)
	Vector Copy Number
Purity	T cell Percentage
	CAR+ T cell Percentage
	Viability
	Appearance
Potency/Function	T Cell Activation
	IFNγ Secretion
Strength	Dose
Product-Related Impurities	Residual Tumor Cells
	Hematopoietic Progenitor Cells
DP Process-Related Impurities	Media components
Vector-Related Impurities	Residual Genomic DNA
	Residual p24
	Residual Plasmid DNA

Stage 1 – Process Design

- A risk assessment (Stage 1) was performed using the critical product quality attributes (CQAs) to identify the potential critical process parameters (pCPPs).
- Potential CPPs were studied as part of multiple process characterization studies to understand the impact of process parameters on product quality and process performance.



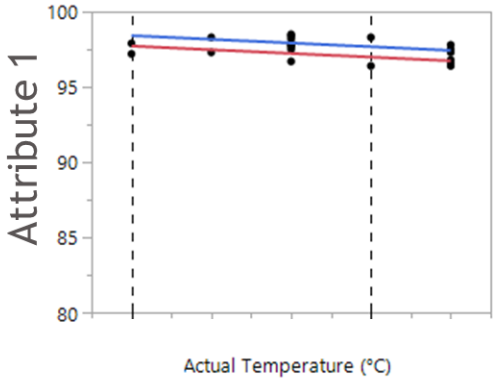
Stage 1 – Process Design

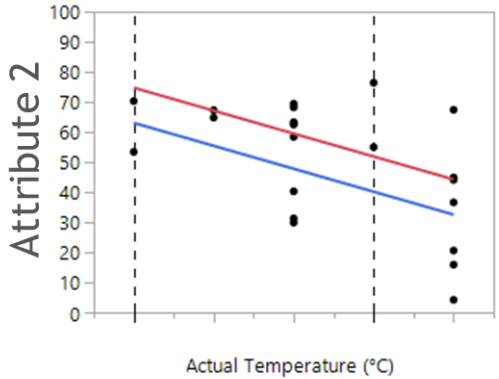
A qualified scale-down model was used to assess the process parameters

- Impact of process parameters on process performance and product quality was assessed
- Factors that had a statically significant effect on the CQAs and exceeded the effect threshold were defined as CPPs

Normal healthy donor leukapheresis material was used to perform the studies

- Helps assess the impacts more robustly than the patient material





Stage 2 – Process Performance Qualification

- **Stage 2a – Risk Assessment**
  - An additional risk assessment (Stage 2a) was performed to define the process parameter controls and their acceptable ranges for the process performance qualification runs.
  - Process parameter controls included:
    - CPPs, nCPPs, IPCs, Hold times and Processing times

- Example Scoring Approach

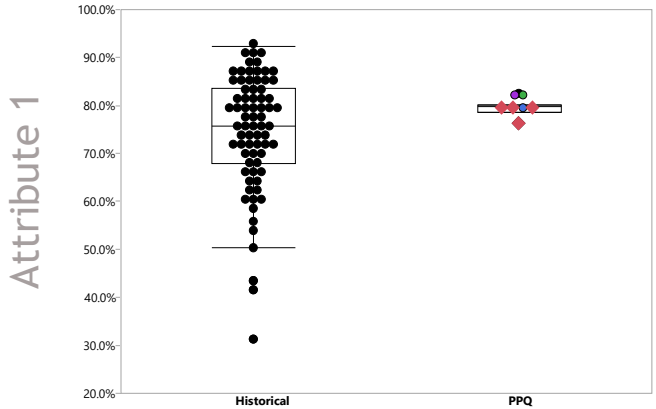
Step	Parameter	Potential Failure Mode	Potential Failure Effects	Potential Causes	Severity	Severity Justification	Occurrence	Occurrence Justification	Detectability	Detectability Justification	Current Controls	RPN	Parameter Classification	CQAs effected
Unit operation 1	Flow rate	Too High	No effect observed during characterization	Operator selects incorrect recipe	1	Shown to have no impact even at extremes	1	Recipe Controlled.	2	Error/fault would occur in case of catastrophic failure.	Recipe driven. LOVO	2	nCPP	None

Stage 2 – Process Performance Qualification

- **Stage 2 – Process Performance Qualification Runs**
  - PPQ batches were executed using the draft control strategy
    - The PPQ combined the facility, utilities, equipment, test methods and the trained personnel with the commercial manufacturing process, control procedures, and components to produce PPQ batches
  - Additional supplemental validation studies were also executed
    - Aseptic Process Qualification
    - Chain of Identity Validation
    - Impurity Clearance Validation
    - Hold Time Studies
    - Filter Validation
  - Overall, control of CQAs was demonstrated by the appropriate combination of control elements: raw material specifications, procedural and process controls, in-process specifications, and the testing strategy (release, stability, and characterization)

Stage 2 – Process Performance Qualification

- PPQ batches demonstrated the capability of the commercial manufacturing process to consistently produce drug product that meets prospectively defined acceptance criteria for critical process parameters (CPPs) and critical quality attributes (CQAs)

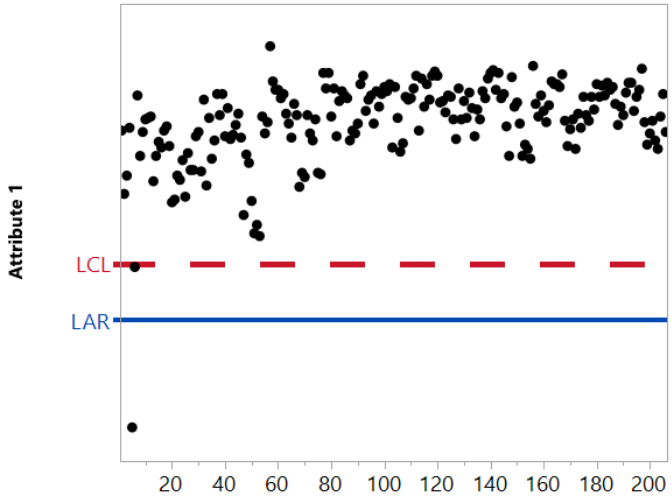


- Following the PPQ runs, a final risk assessment (Stage 2b) was performed to define the process parameter controls and their acceptable ranges for the proposed commercial control strategy.
  - Process capability, knowledge from the additional validation and characterization studies were considered in this final risk assessment

Continued Process Verification (CPV)

Goal of CPV is to provide constant assurance that the process remains in a validated state of control.

An additional risk assessment was performed to identify the process parameters/attributes that will be monitored during the commercial manufacture of drug product along with the respective control limits during CPV.



LCL = Lower control limit

LAR = Lower Acceptable range

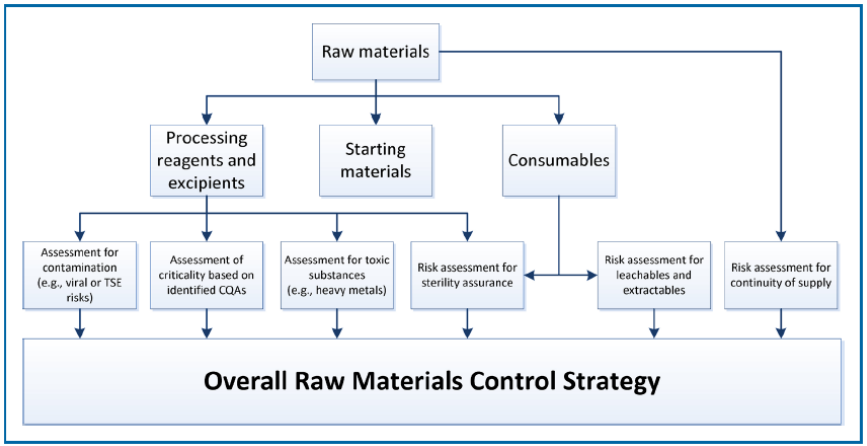
Raw Materials Control

All raw materials were assessed for

- suitability of use in the manufacturing process (impact to CQAs)
- Adventitious agents (Viral and TSE risks)
- Extractables and leachables (consumables)
- Continuity of supply

Appropriate incoming release specifications were defined that included

- Appearance
- Identity
- etc.,



- PDA TR81

Testing Strategy

Validated methods were used for release testing of the final drug product

Stability testing was performed as per ICH Q5C guidelines to shelf life for the drug product was established

Routine in-process testing is performed as part of the lot manufacture

Extended characterization testing was performed to demonstrate process comparability

- Example Control Strategy

Category	Attribute	Testing Strategy
Safety	Sterility	Release
	Mycoplasma	Release
	Endotoxin	Release
	Replication Competent Lentivirus (RCL)	Release
	Vector Copy Number	Release
Purity	T cell Percentage	Release
	CAR+ T cell Percentage	Release, in-process
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	Appearance	Release
Potency/Function	T Cell activation	Release
	IFNγ Secretion	Characterization
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Product-Related Impurities	Residual Tumor Cells	Characterization
	Hematopoietic Progenitor Cells	Characterization
DP Process-Related Impurities	Media components	Characterization
Vector-Related Impurities	Residual Genomic DNA	Characterization
	Residual p24	Characterization
	Residual Plasmid DNA	Characterization

Conclusion

Despite the accelerated development pathway for the cell-therapy product, a risk-based approach considering product, process and facility knowledge was used to develop a robust control strategy

Similar approach was taken to develop the control strategy for the vector (critical raw material in the drug product manufacturing process)

All key elements of control strategy were considered to develop and validate the commercial manufacturing process

Thank you

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