Considerations in Validating Car T Cell Therapy Manufacturing Processes

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Overview

- CAR T Cell product development/CMC timeline considerations
  - Comparison with Biologics product development
- Manufacturing Process development
  - Considerations and challenges
- Manufacturing Process validation
  - Application of existing validation guidelines for a late stage cell therapy product (JCAR017, lisocabtagene maraleucel)
- Future opportunities/Life cycle management of cell therapy manufacturing processes
  - Process control considerations

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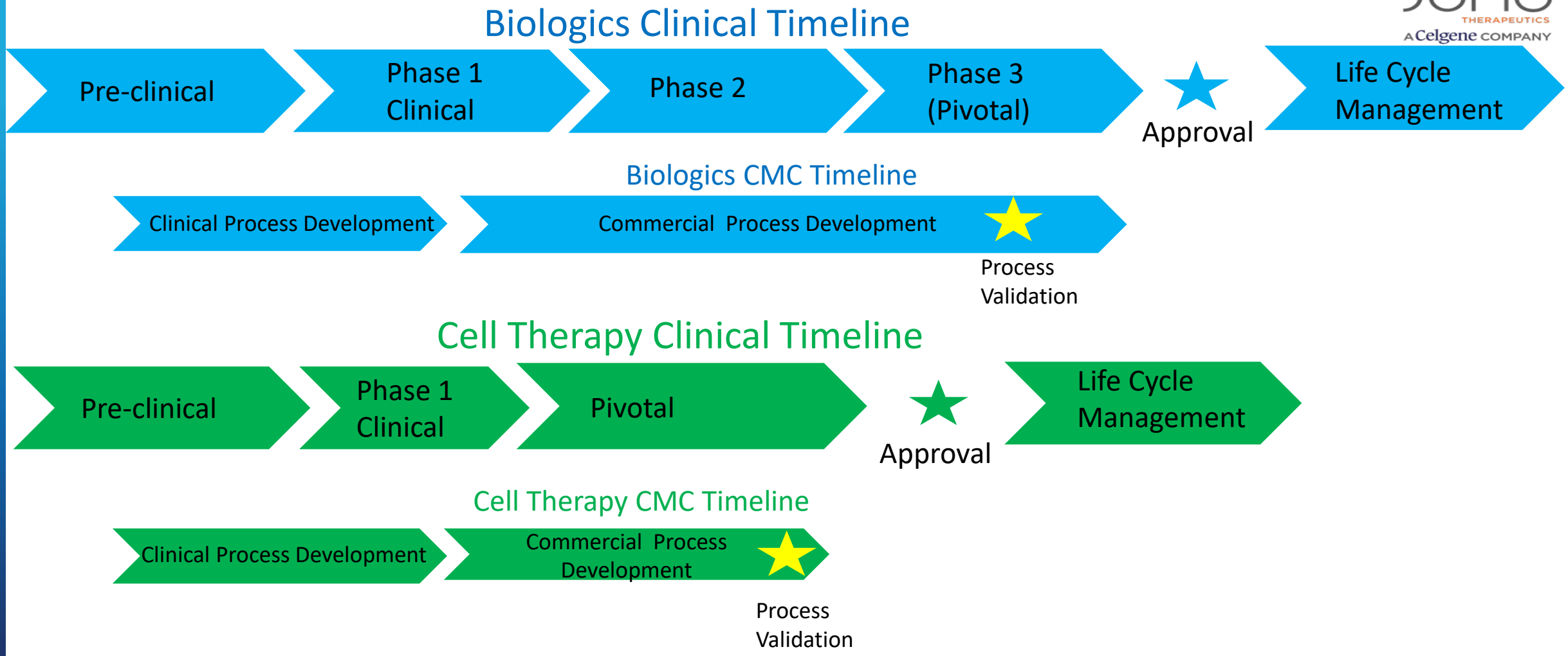
Product Development – Exemplary Timeline Considerations



- Cell Therapy Product development → may be significantly shorter than traditional biologics program
  - Shortened timelines require more rapid development of commercially viable/robust processes

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CMC Development Considerations: Biologics and Cell Therapy

Development Consideration	Well Characterized Biologics (e.g. mAbs)	Cell Therapy
Product understanding	CQAs typically well defined. Link between product and process well established.	Attributes impacting product safety, efficacy and potency early stage of understanding
Manufacturing Process	Platform unit operations	Technology continuing to evolve
Starting Material	Well characterized and consistent (WCB)	Every batch unique and can drive process/product quality variation
Raw Materials	Platform, chemically defined, animal- free	Ancillary Materials (animal-derived) may be required to support human T cell growth
Clinical Manufacturing Experience (prior to validation)	Variable (product/process-specific)	Significant (one batch = one patient)

- Cell therapy product/process understanding at an early stage
  - CQA/critical process parameter determination heavily dependent on clinical outcomes
- Cell therapy process development and process control considerations
  - Every batch is unique – requires a robust and/or flexible control strategy to ensure product/process consistency
  - Starting material variation – complicates process/analytical development and validation
  - Use of Ancillary raw materials (e.g. cytokines, albumin) may be required to support T Cell manufacturing

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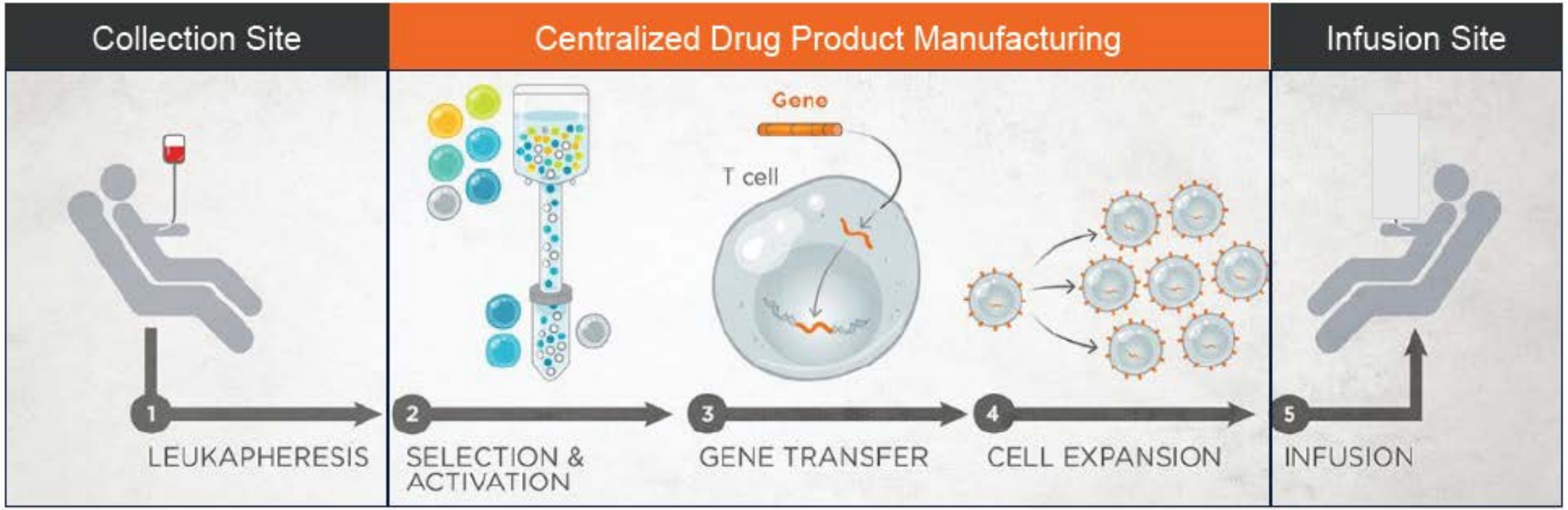
Exemplary Manufacturing Process: JCAR017[1]



- JCAR017, lisocabtagene maraleucel: CD19-directed CAR T cell product with a highly controlled manufacturing process
- Manufactured from autologous T cells
- Enables administration of a defined composition of $CD8^+$ and $CD4^+$ CAR^+ T Cells
- Resulting composition characterized for > 100 phenotypic, functional and cell health-related quality attributes
- Subsets of attributes identified as being CQAs

JCAR017 is an investigational product not yet approved by regulatory authorities in any country.

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[1]Ramsborg, ASH, 2017

Cell Therapy Manufacturing Process Validation Approach

- Follow the 2011 FDA process validation guidance (3 stage design)[1] with the following notable considerations

- **Stage 1: process design – define the commercial process through process development**
  - Selection and use of starting material
  - Clinical manufacturing experience
  - Identification and measurement of known/potential CQAs

- **Stage 2: process qualification – demonstrate process is capable of reproducible commercial manufacturing**
  - Justification of starting material
  - Number of qualification batches
  - Components (raw materials)

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[1]FDA Guidance for Industry, Process validation: General Principles and Practices, Jan, 2011

Cell Therapy Manufacturing Starting Material Considerations

- **Starting material derived from healthy donor cells used in support of process development and performance qualification**
  - Lack of available patient material

- **Healthy donor model justification includes the following**
  - Demonstrate manufacturing process controls ensure that CQAs are maintained within consistent and controlled levels despite substantial variations in starting material attributes
  - Assessment based on product quality comparison between starting materials derived from healthy donors and patients (clinical experience)

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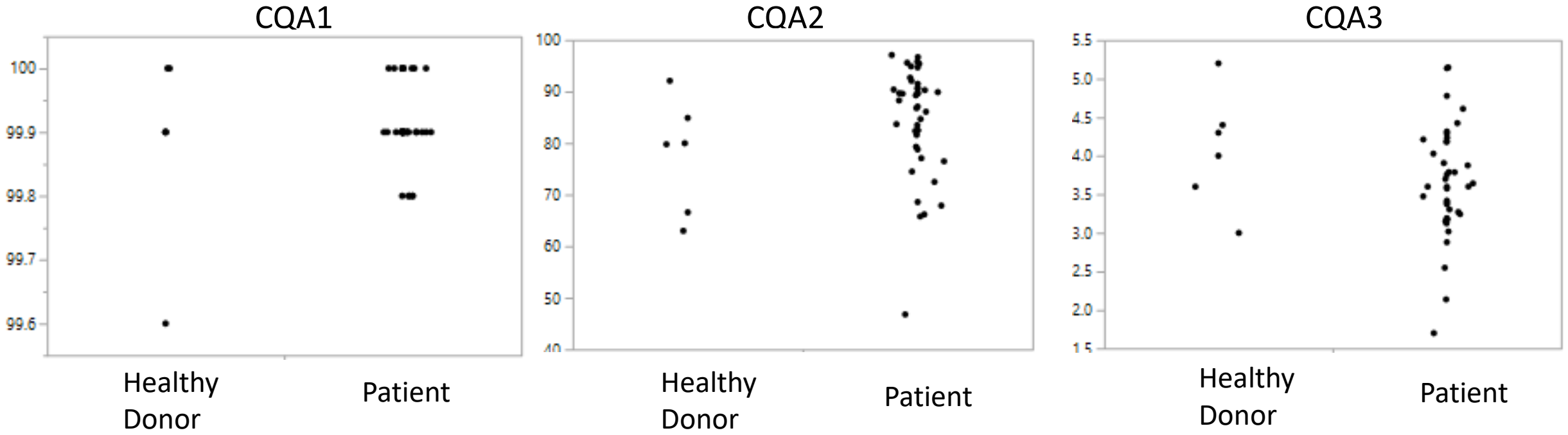
Engineered Cell Composition CQAs: Batches Using Healthy Donor and Patient Starting Materials



- Manufacturing process produced drug product CQAs with similar ranges and within release specifications despite substantial variations in the starting material attributes
- Healthy donor material used in lieu of patient material in support of process development and process qualification

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Process Qualification Approach

- Provide confidence that the process is capable of generating a reproducible commercial product[1]
- Risk-based approach and assessment used to determine and justify number of batches to support process qualification
- Four areas considered as part of the risk assessment
  - Product knowledge
  - Process understanding
  - Control strategy
  - Facility/equipment controls and capabilities
- Knowledge assessment tool used to assign weighted risk factors in four areas
- Overall risk score calculated and used to determine the recommended number of PPQ runs

[1]FDA Guidance for Industry, Process validation: General Principles and Practices, Jan, 2011

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Risk Assessment Areas and Considerations for PPQ Strategy

Risk Assessment Area	Description
Product Knowledge	Drug product knowledge and CQA variations that could impact clinical outcomes, such as safety, efficacy, and pharmacokinetics
Process Understanding	Understanding relationship between process parameters and impact to product quality, including raw material variations
Control Strategy	Level of process controls in place for controlling process variability
Facility/Equipment	Facility/Equipment controls and capabilities at the intended commercial manufacturing plant

- Overall risk score calculated from the four areas and used to determine the recommended number of batches to support process qualification
- PPQ design also accounts for variations related to manufacturing process, component variability and analytical variability

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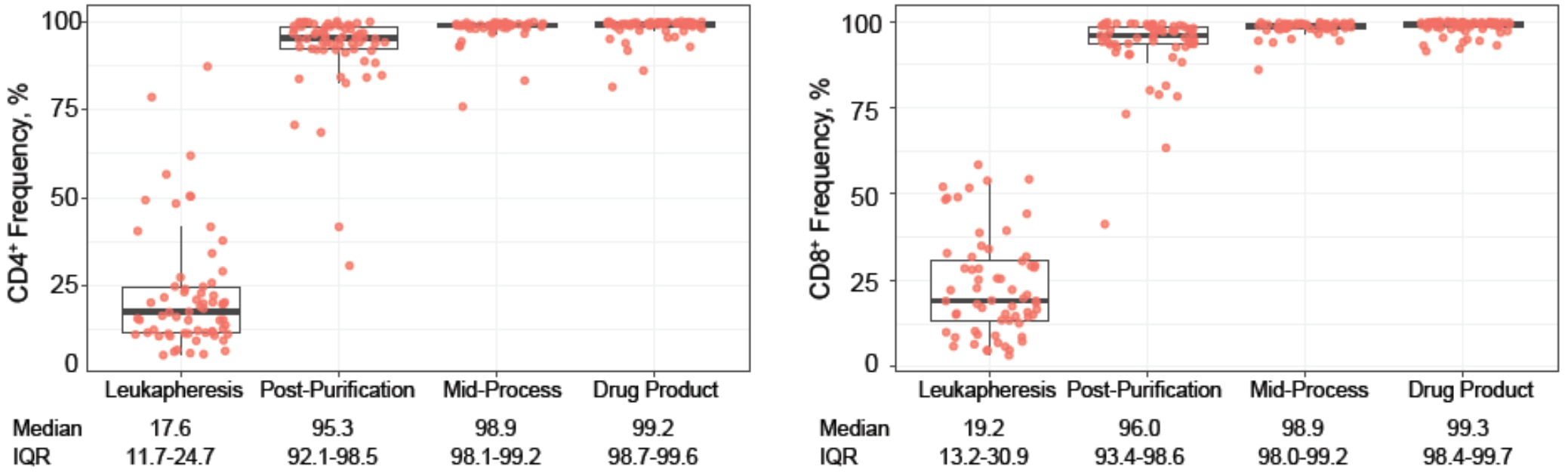
Lifecycle Management Considerations: Advanced Process Control

JCAR017 CD4+ and CD8+ Purity by Process step[1]



- Manufacturing success critical for patients → strive for 100% success rate
- Variable nature of the starting material presents a challenge
  - Variable drug product quality → potential impact on product
  - Potential for process inconsistency (e.g. process duration)

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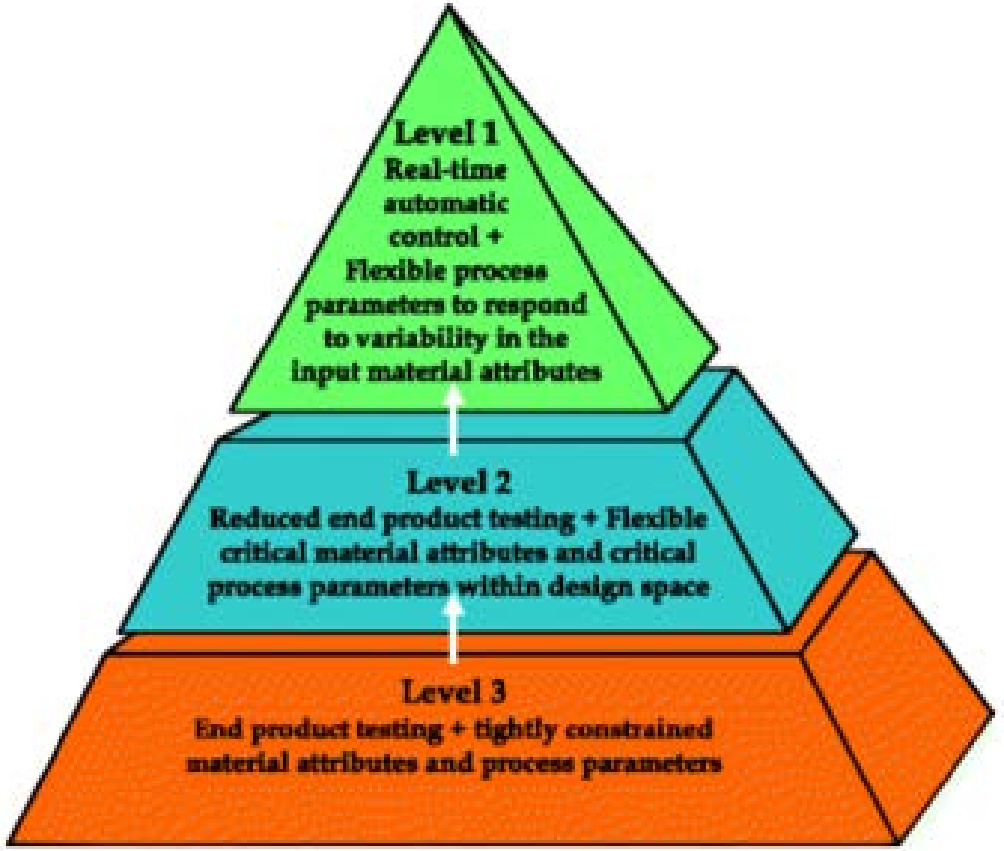
Process Control: Current and Future State

Current State:
Control parameters at set point



Understanding Pharmaceutical Quality by Design
Yu et al, The AAPS Journal, 2014

Future State:
Flexible process parameters to respond to starting material variation

- Adaptive process control
  - Enables capability to adjust the manufacturing process based on incoming or in-process measurements of product/process attributes
  - Technologies and capabilities from the biologics industry potentially applicable to cell therapy manufacturing processes to enable adaptive process control

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Summary

- Successful development and validation of autologous cell therapy process poses some unique challenges
  - Aggressive development timelines (Phase 1 → Pivotal)
  - Variability and availability of starting material
  - Product and process understanding in its early stages
- Several process development strategies employed to support the validation of a late-stage autologous cell therapy product
  - Manufacturing process controls in place to ensure that CQAs are maintained within consistent and controlled levels despite substantial variations in starting material attributes
  - Justification and use of healthy donor starting material in support of development and process qualification
- Employ a risk-based approach as part of PPQ design and batch number justification
  - PPQ design should also account for variations related to manufacturing process, component variability and analytical variability
- Adaptive control strategies from the biologics industry potentially applicable for future cell therapy processes
  - Design the control strategy to account for variability in starting material attributes

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