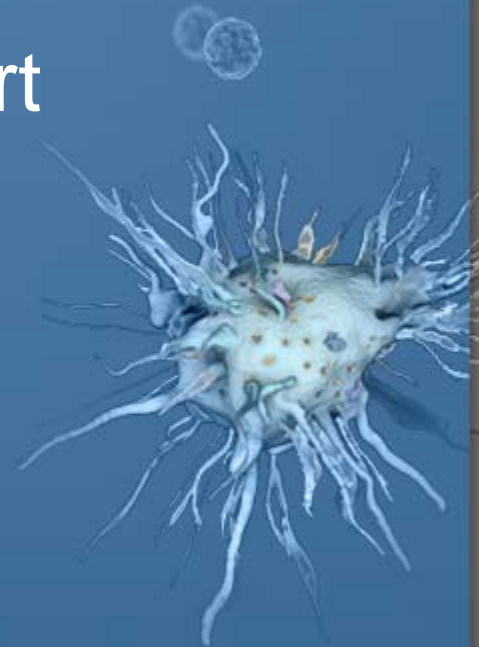


Development and Validation of a Cellular Therapy Product to support Regulatory Applications and Commercial Supply

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Discussion Agenda

- Product Description and Manufacturing Overview
- CMC Strategies to Support Regulatory Application and Commercial Operations
 - Product Development and Validation Lifecycle
 - Manufacturing Controls and Product Testing

Preparing for Commercialization

- Develop a Product Life Cycle plan that integrates operational, technical, compliance, and regulatory requirements
 - Increasing Manufacturing Capacity
 - Change in Manufacturing Facility and/or Site
 - Reducing Cost of Goods
 - Second Sourcing Vendors
 - Manufacturing Process Improvements
 - Analytical Method Improvements
 - Changes to Product Specifications
- Many of these type of changes require years to implement and may require extensive testing, regulatory submissions, or additional clinical trials
- Thorough product and process characterization facilitates evaluation and implementation of changes

Product Description

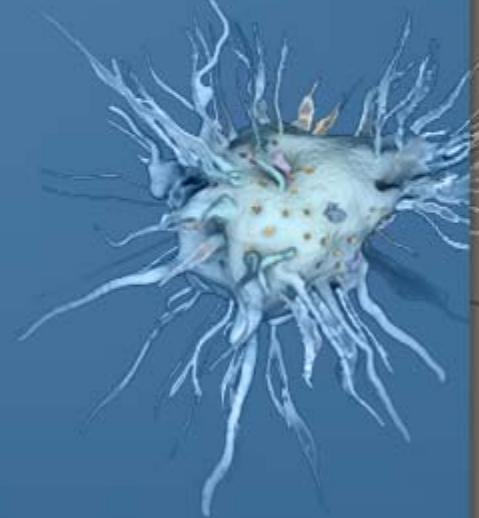
- Cellular immunotherapy for the treatment of prostate cancer
- Autologous, apheresis-derived, mononuclear cell preparation containing activated antigen presenting cells (APCs)
- Aseptically processed utilizing single-use, disposable tubing sets and devices
- Supplied in a sealed bag for patient-specific infusion
- Key Attributes include CD54 upregulation on APCs and CD54+ Cell Count

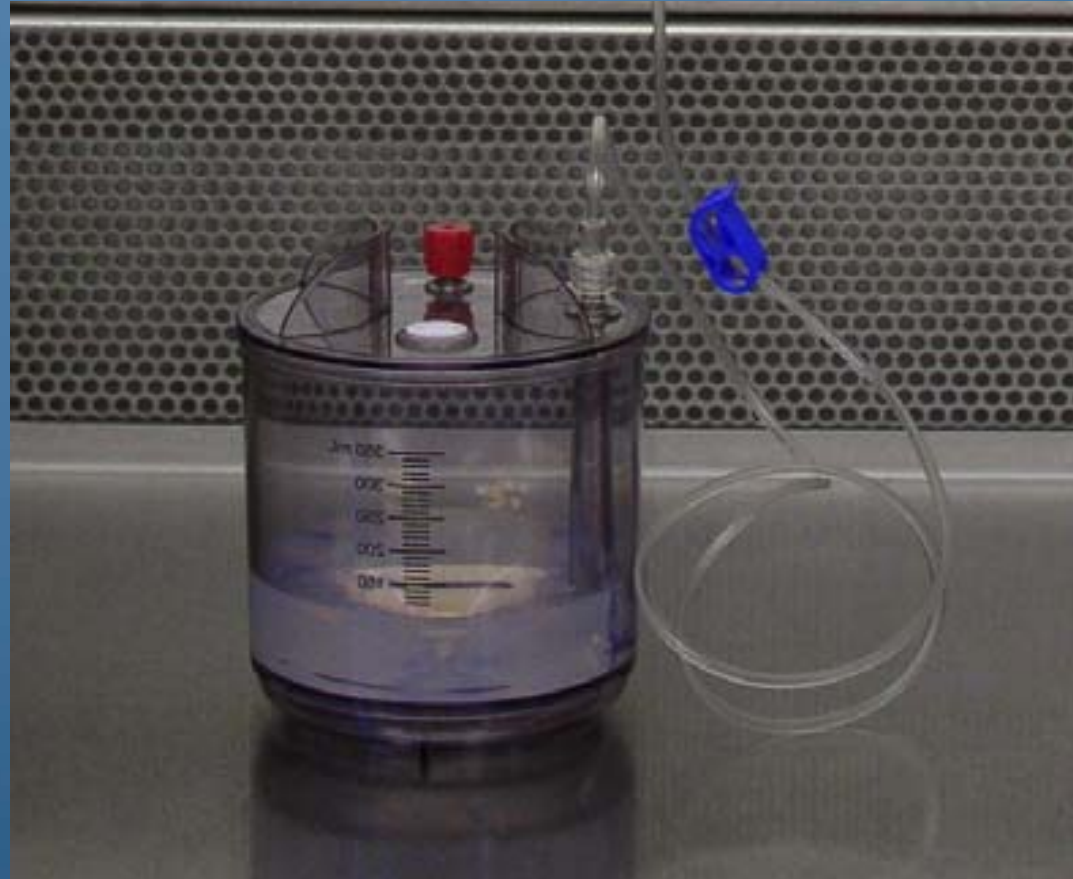
Manufacturing Process

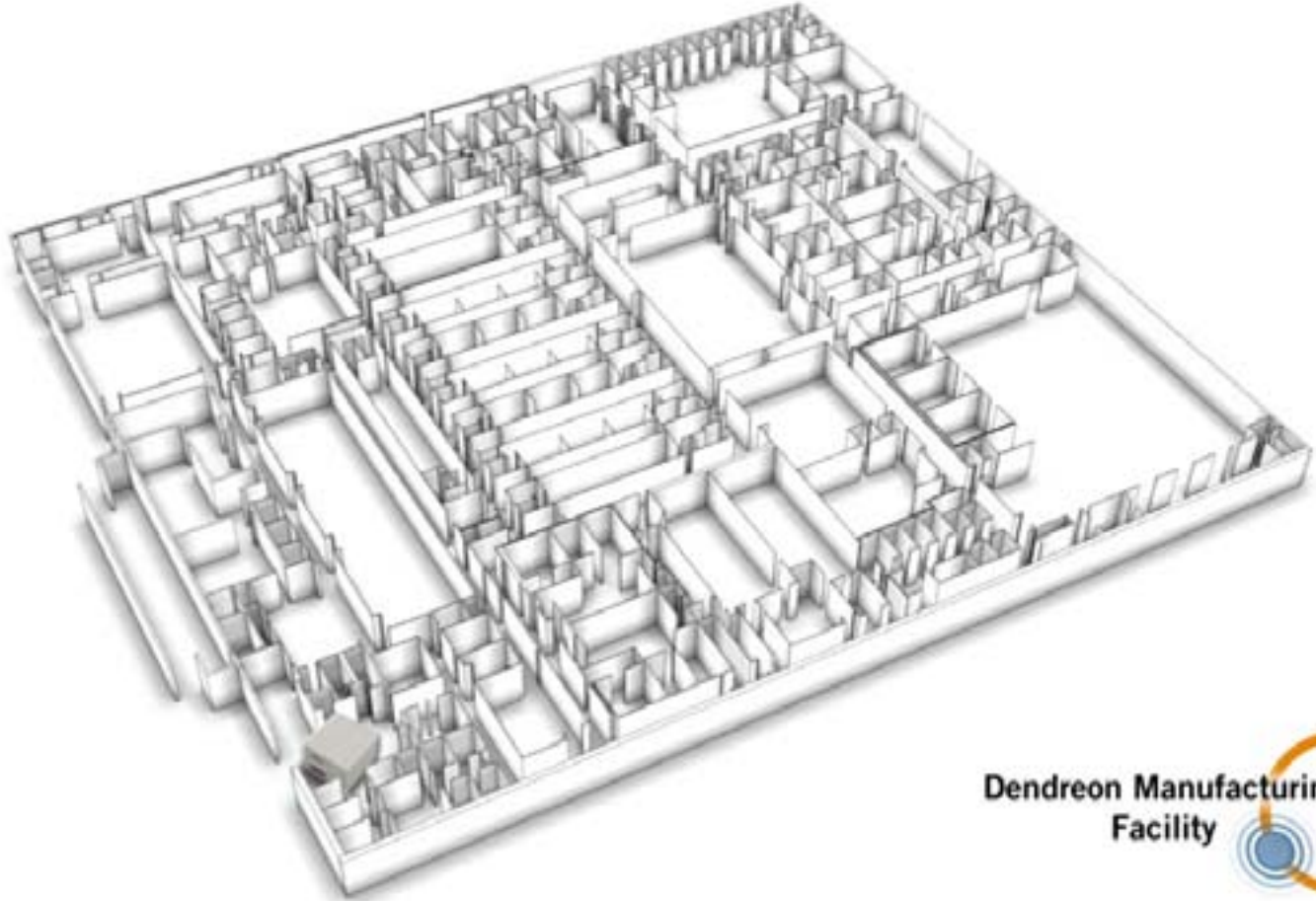


Features of Manufacturing Process

- APH starting material
- Devices to handle large volumes of cell suspensions
- Buoyant density solutions (BDS)
- Recombinant protein antigen
- Single use, disposable tubing and devices
- QC testing at multiple places within the process







**Dendreon Manufacturing
Facility**

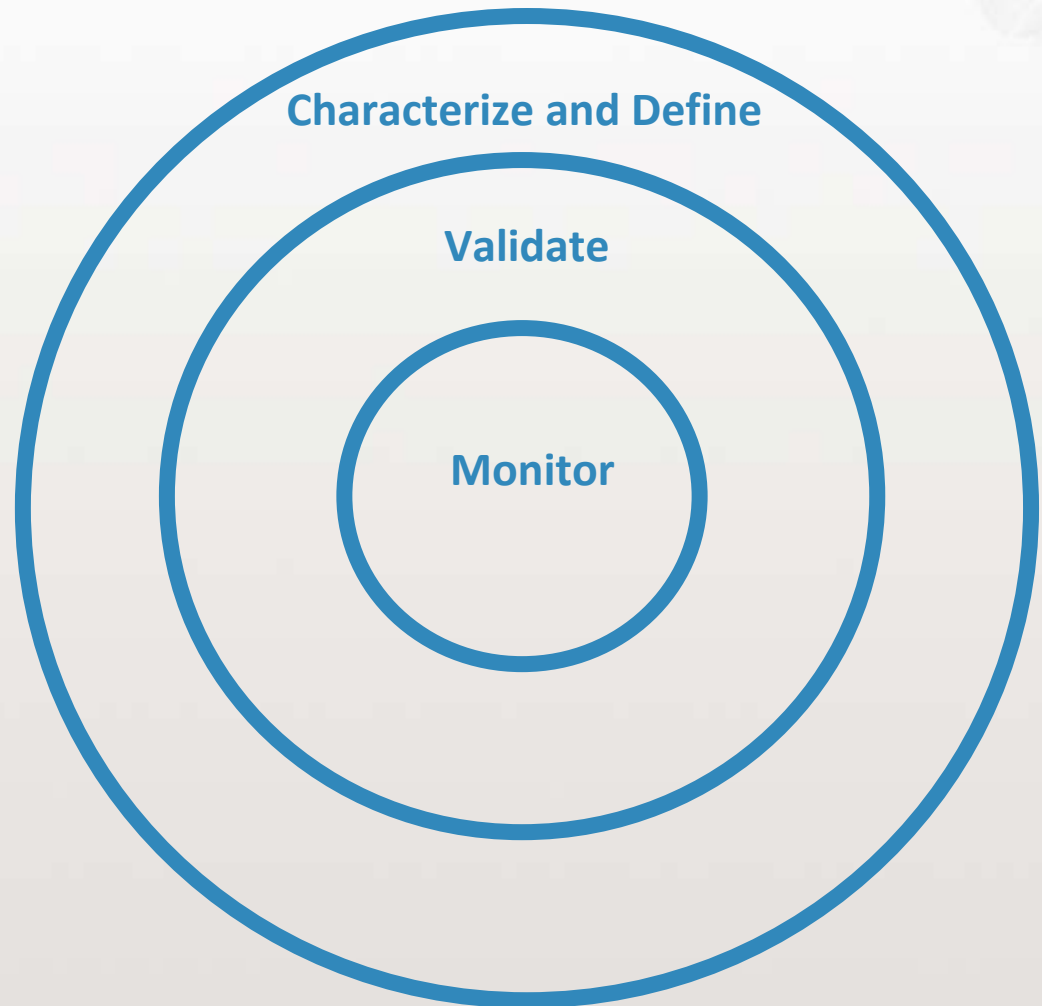




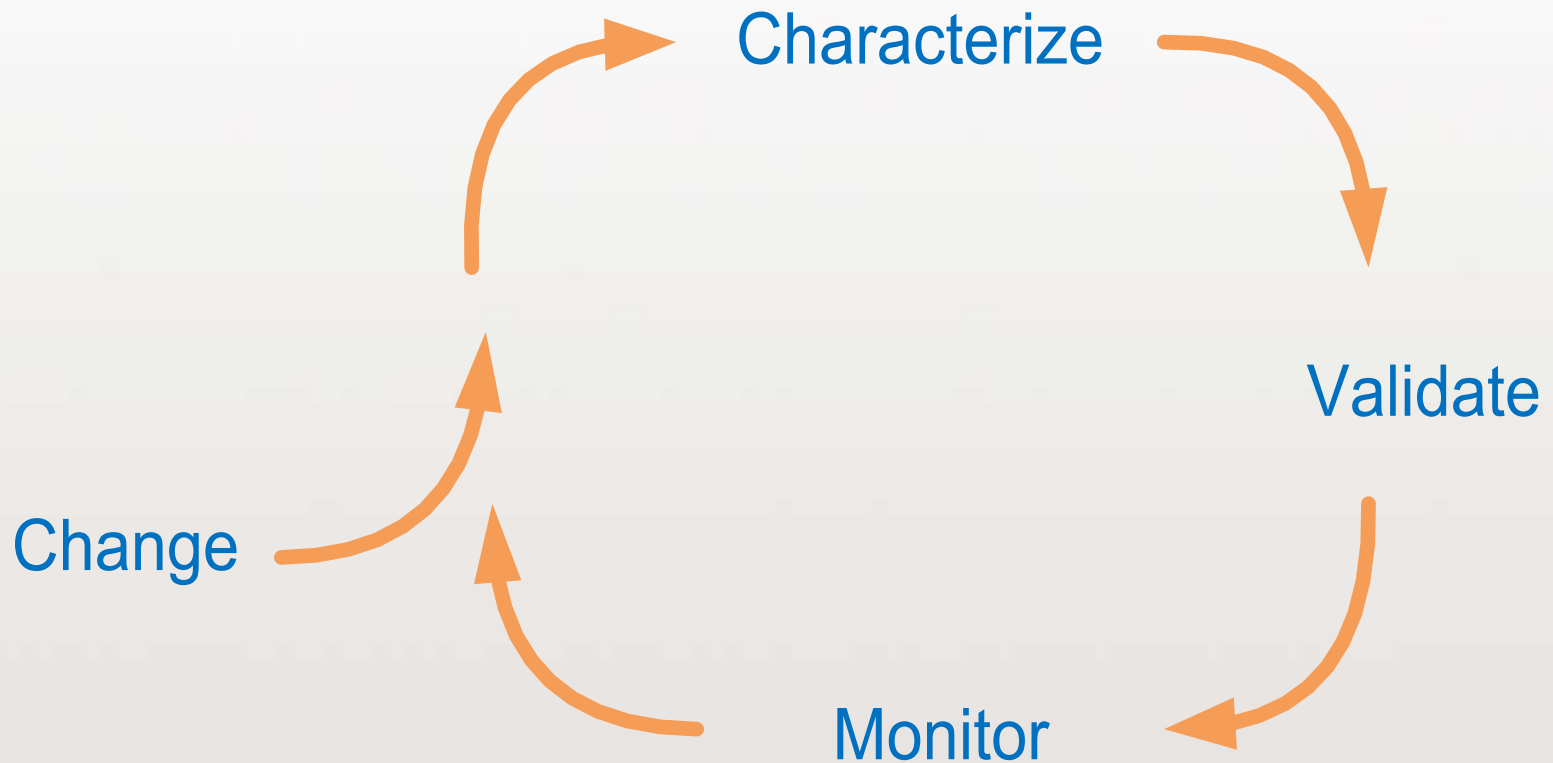


Product Development and Validation Lifecycle

- **Characterize and Define**
 - Process Development and Characterization
 - Detailed Process Description
- **Validate**
 - Process Consistency
 - Clearance of Residuals
 - Process Times
 - Aseptic Process
 - Cleaning and Sanitization
 - Transport
- **Monitor**
 - Commercial Manufacturing Process Monitoring and Trending



Development and Validation Lifecycle



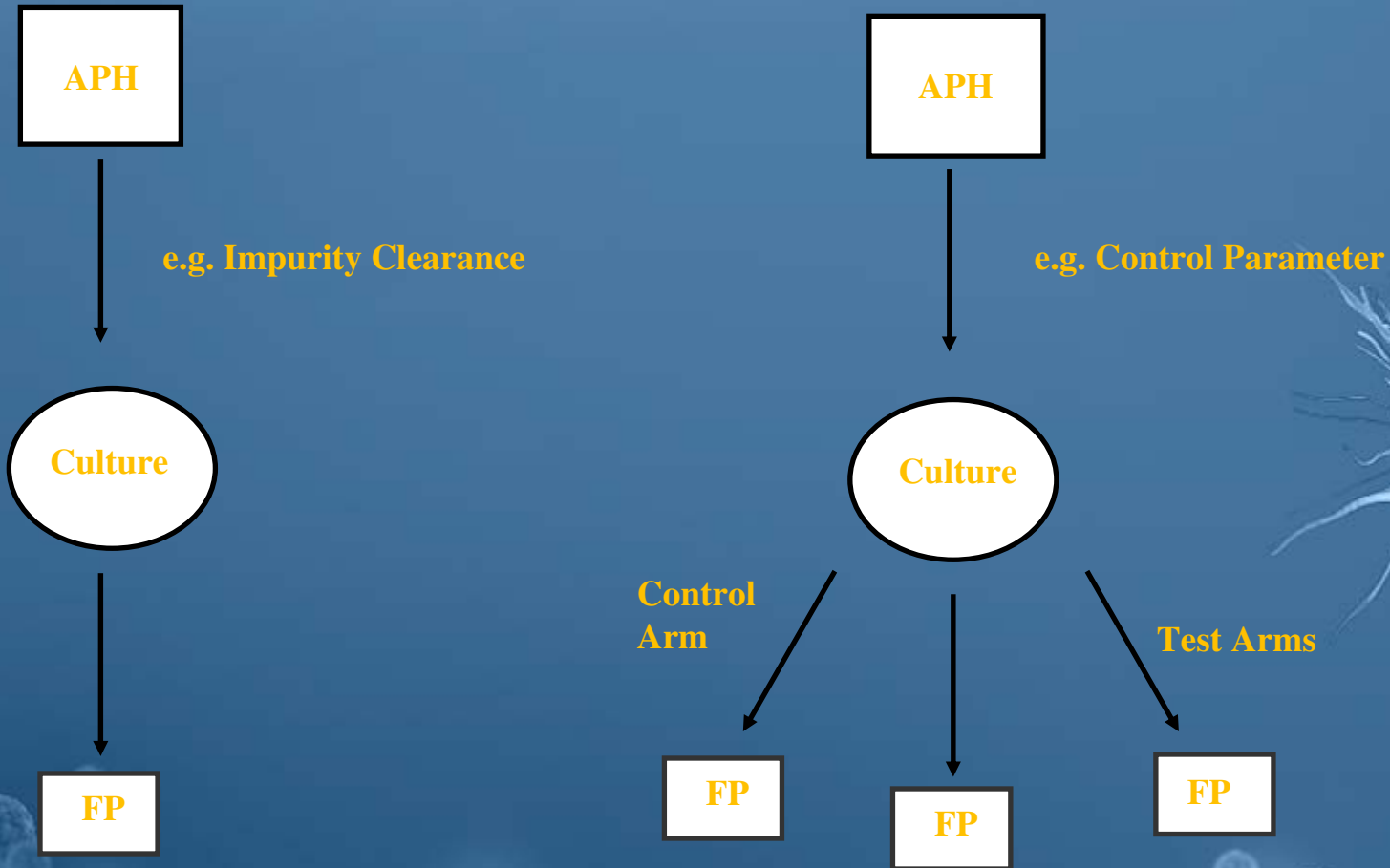
Process Characterization Studies

- Increase process knowledge
- Determine set points, ranges, and critical parameters
- Define manufacturing steps, capabilities, and process parameters
- Provide consistent approach
 - Operation Control Parameter (input)
 - Process Performance Parameter (output)

Process Model System

- “Pilot Scale” representative of “Full Scale” manufacturing
 - “Healthy Donor” cells in place of “Patient” cells
- Qualified system allows for quantitative conclusions
- Used for process characterization and trouble shooting
- Defined model for pre-approved study protocols
- Repeatable and reproducible

Study Design



Parameters

- Operation Parameters
 - Incubation temperature
 - Antigen concentration
 - Culture volume
 - Culture time
 - CO₂ level
 - Hold time
 - Centrifuge speed
 - Centrifuge temperature
 - Wash volume
- Performance Parameters
 - Composition (cell types)
 - Surface marker upregulation
 - Step yields (cell numbers)
 - Cell viability
 - Impurity clearance

Characterize

- Provide process thumbprint with unit operations
- Identify operational parameters based on experience
- Identify critical parameters
- Link performance parameters to product attributes
- Execute process characterization studies according to pre-defined protocols
- Document results in Development Reports
- Identify parameters for Process Validation

Process Validation

- Manufacturing Process Validation
 - Utilize Healthy Donor cells
 - Specify Acceptance Criteria
 - Process Characterization Studies
 - Historical Experience
 - Demonstrate Reduction of Impurities
 - Demonstrate Consistently Meets Process Performance Criteria
 - Demonstrate Consistently Meets Product Specifications

Manufacturing Process Validation

- Protocols executed at “scale” following approved procedures
- Execute at to be commercial facility utilizing validated analytical methods, facilities, and equipment
- Manufacture at nominal control points
- Demonstrate process consistency, control, and performance
- Meet Product Specifications

Examples

- Note that sipuleucel-T has been in Phase 3 clinical development for over 10 years
- Adjust and evolve your approach concurrent with changes and additions in regulations and guidance

Multiple Manufacturing Sites

- Are the products from the multiple manufacturing sites utilized for the phase 3 studies the same?
- Is the product from the to be commercial manufacturing site the same?
- Can the product from the future manufacturing sites be demonstrated to be the same such that new clinical trials are not required for new manufacturing sites?

Multiple Manufacturing Sites

- Demonstrate Product Comparability through comparison of GMP systems as well as through Product Characterization:
 - Systems: Equipment, Raw Materials, Procedures, IPC/Specifications, Test Methods, Trending, Training, Quality
 - Characterization: utilize comparability approach similar to that for “specified biologics”
 - ICH and FDA Guidance
 - Utilize a statistical method that’s appropriate for product characteristics

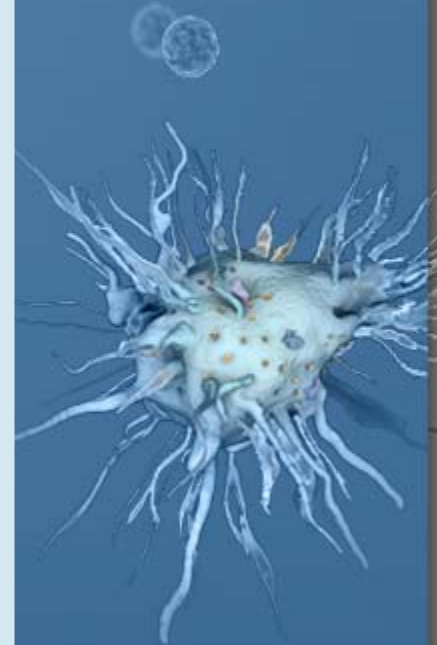
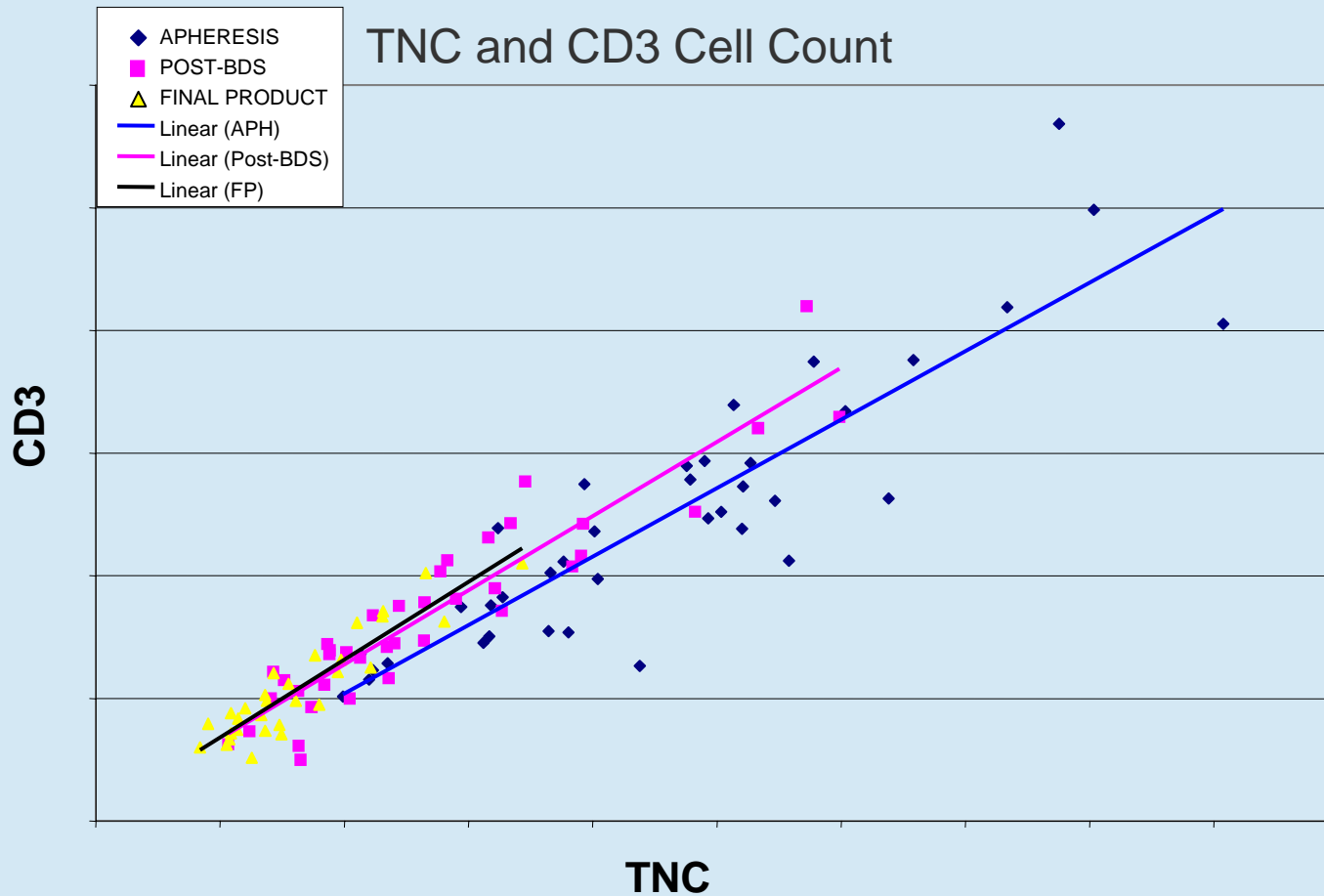
Product Testing

- Broad testing during early development
- May have an attribute(s) within your specification that has been determined to be no longer required to measure on a lot by lot basis
- May not “scale” well when testing at a “large scale” volume of patients
- Attribute may consistently be well within specified range

Approach

- Characterize process and product
- Demonstrate process capabilities
- Determine correlation between various attributes tested in the final product
- Continue to measure broader attributes when testing in support of process validation associated with new facilities or significant process changes

Correlation of Attributes



Summary

- Applied a “well characterized biologic product” approach
- Thorough process characterization demonstrates process capabilities and provides the process definition
- Facilitates Process Validation, supports Regulatory Submissions, and ability to determine impact of Changes
- Allows for increased space to implement Commercialization Strategies