Cell Therapy Product Manufacturing Considerations

An ECI Conference Series

Scale-up and Manufacturing of Cell-based Therapies V

Collaborating with Regulatory Agencies to Define the Landscape for Emerging Cell-Based Therapies – Challenges and Lessons Learned

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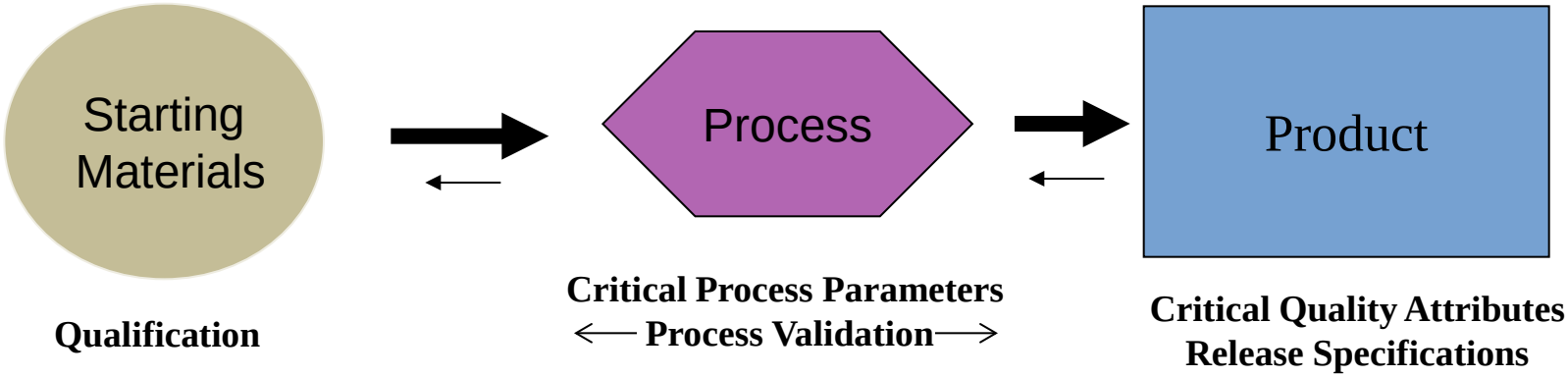
Overview

- Establishing Manufacturing Control
  - Applying Principles of Current Good Manufacturing Practices
  - Knowing the Product
    - Understanding Product's Critical Quality Attributes and Critical Process Parameters
- Knowing How to Deal with Process Change
  - How to Establish Product Comparability

Challenges: Cellular Products

- Batch to Batch Consistency in Cell Manufacturing
  - Starting Material
    - Donor to Donor Variations
  - Product is Defined by a Process
    - Critical Process Parameters
  - Product Quality
    - Critical Quality Attributes
    - Challenging to Establish In Vitro Assays Predictive of Product Activity/Potency



Consistent and High Quality Product Manufacturing

- Current Good Manufacturing Practices (CGMP)
- Knowledge of Product

CGMP Considerations for Cell Therapy Products

- As cell therapy products are maturing the CGMP considerations become more critical to product safety and efficacy
  - Guidance to Industry

    - **CGMP for Phase I Investigational Drugs published in 2008**

    www.fda.gov/downloads/**Drugs**/.../Guidances/ucm070273.pdf

Key Principles of CGMP

- **CGMP is set of good manufacturing practices which assure;**
  - Quality of product (investigational and approved/licensed)
    - Prevent cross contamination
    - Prevent product contamination with foreign matters
  - Manufacturing consistency of high quality product

Full CGMP Requirements (Licensure)

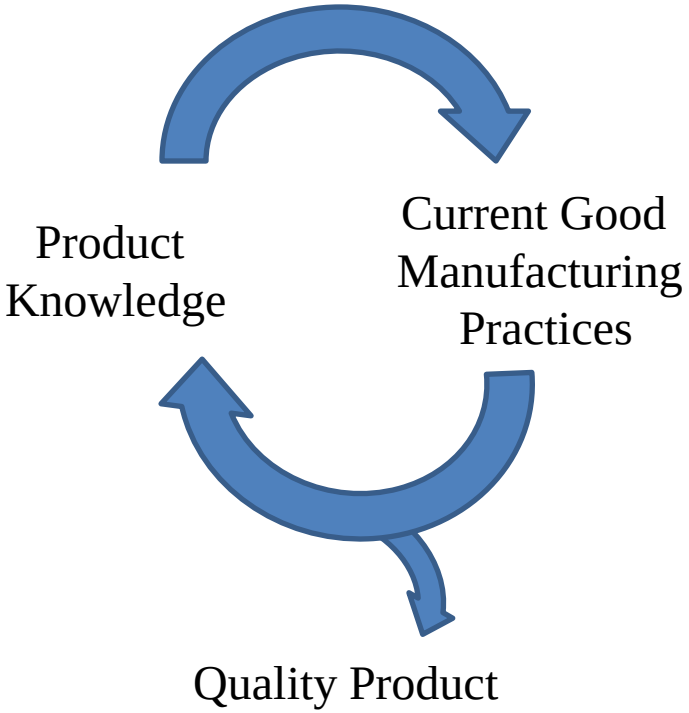
- CGMP is verified at the time of Pre-License Inspection during BLA review
- Compliance with Applicable Regulations
  - PHS Act, Section 351 (a)(3)(c) and FD&C Act
  - Federal Regulations - 21 CFR:
  - 210s & 211s – Current Good Manufacturing Practice Regulations (CGMP)
  - 600s,- Biological Products
  - 1271s – Human Cells, Tissues, and Cellular and Tissue-Based Products

Examples of Inspection Issues Identified

- Inadequate Quality System
  - Quality Control Unit (QCU) lacks responsibility and authority
  - Lack of procedures and documentation
  - Instances of no QCU oversight
- Incomplete process validation and validation of aseptic processing
- Batch record documentation – lack of detailed process descriptions
- Lack of cross contamination control such as inadequate space for operations, monitoring of the facility, and inadequate segregation of quarantine materials
- Inadequate label reconciliation
- Inadequate Standard Operating Procedures, Change Control, and Investigations
- Not closing out investigations in a timely fashion

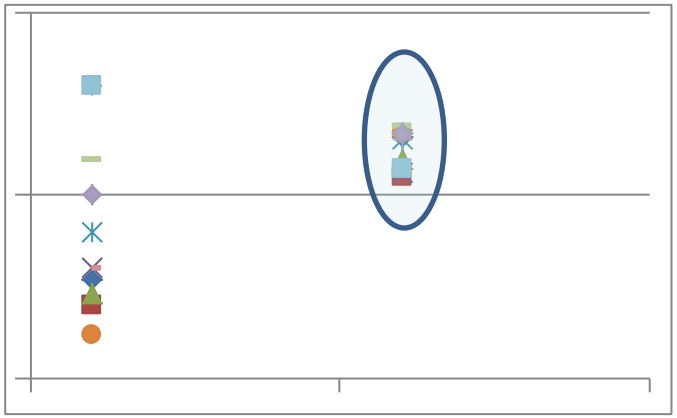
Consistent and High Quality Product Manufacturing

- Current Good Manufacturing Practices (CGMP)
- Knowledge of Product



Knowing Your Product-Tools for Establishing Manufacturing Consistency

- Critical Quality Attributes (CQA)
  - Identity, purity and potency
- Critical Process Parameters (CPP)
  - Key manufacturing steps critical to product quality
- Risk Assessments (RA)
  - Linkage between product quality, CQA and CPP

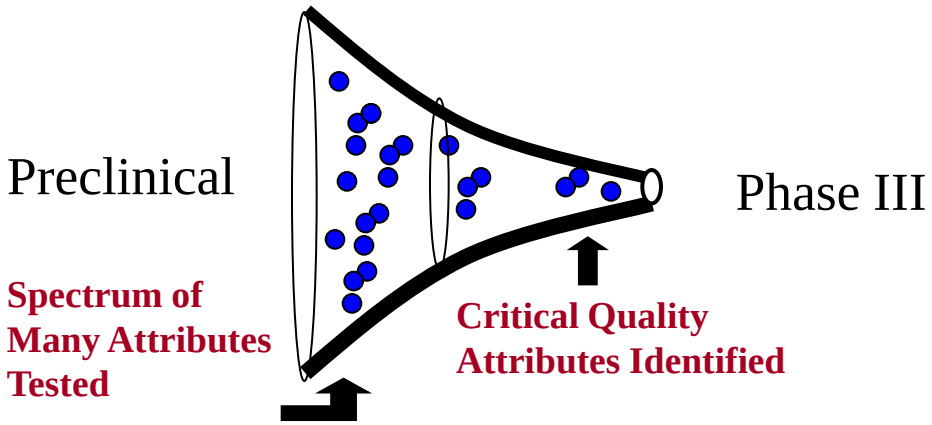


Threshold

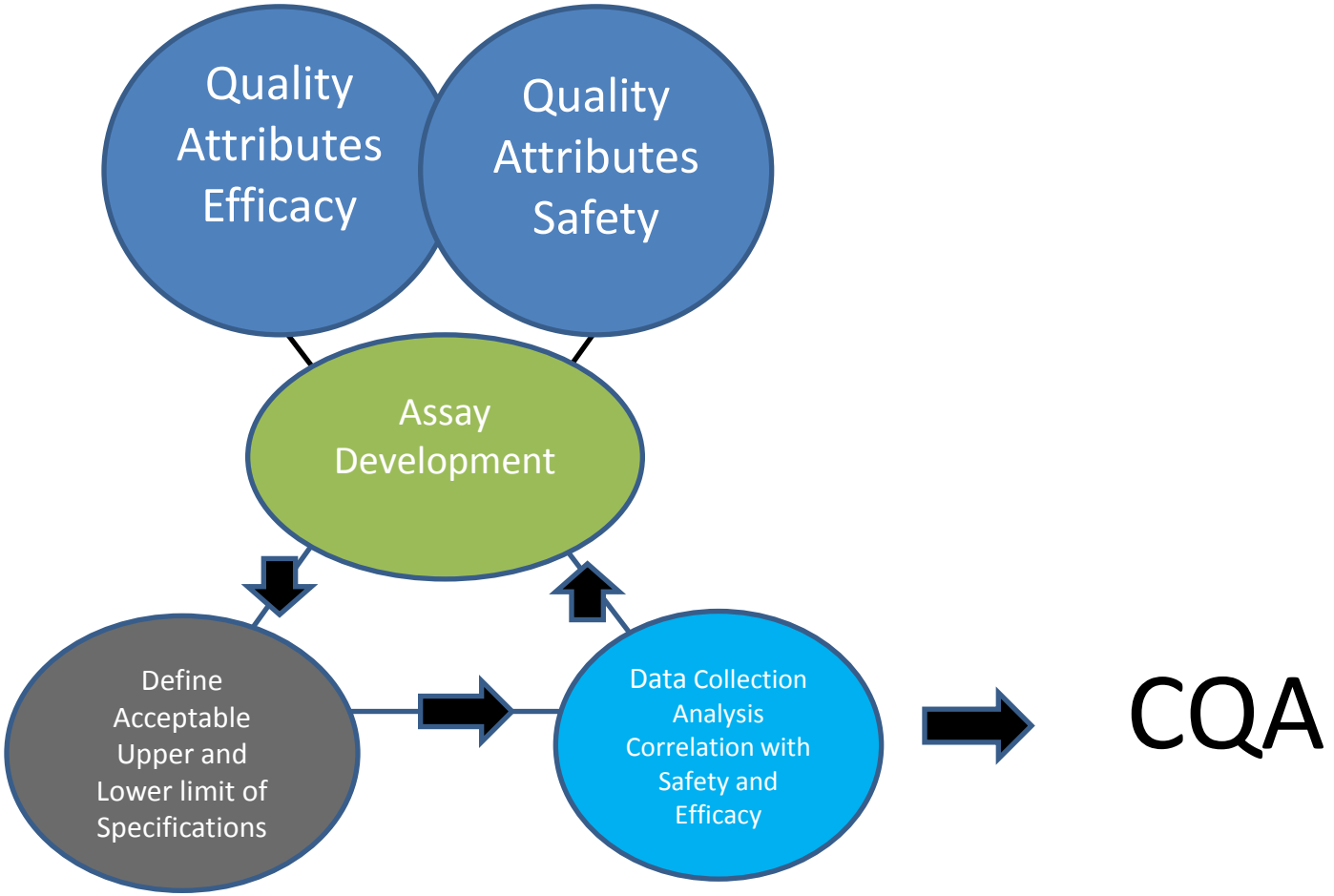
Manufacturing inconsistency as a confounding factor for showing product safety and efficacy

Critical Quality Attributes (CQA)

- CQA are biological and molecular characteristics that could be useful in determining product quality
- Can these attributes be properly defined for biologics?
  - Often difficult due to complexity of biologic products
  - Typically evaluate many attributes early during development and narrow down or refine during lifecycle
    - Purity, potency and other relevant physical and biological characteristics



Identifying Critical Quality Attributes is an Iterative Process



Assay Development Considerations During all Stages of Clinical Trial

- What is being tested?
- What is a suitable Assay?
  - Sensitive, Accurate
- Is the method appropriate?
  - Is it the right method to measure the relevant analyte?
- Is the method under control?
  - If you ran the same sample again, would you get the same answer?

Defining Meaningful Specifications

- 21 CFR 211.160 (b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.
- Identify upper and lower limits
  - Based on historical data
  - Inherent variability of the assay
- Identify sources of process variability
- Reduce variability iteratively

Critical Quality Attribute Measurement- Potency

21 CFR 600.3(s):

…potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result

- Interpretation:
  - Every lot you release will have the similar potency profile as lots used in the clinical studies conducted to determine the drug product efficacy
  - Clinical data obtained may be useful in defining product potency and to validate suitability of the potency assay to measure product efficacy

21 CFR 610.10:

…shall consist of either in vitro or in vivo tests, or both, …specifically designed for each product... to satisfy the interpretation of potency given by the definition in 600.3(s) of this chapter

Establishing a Potency Assay

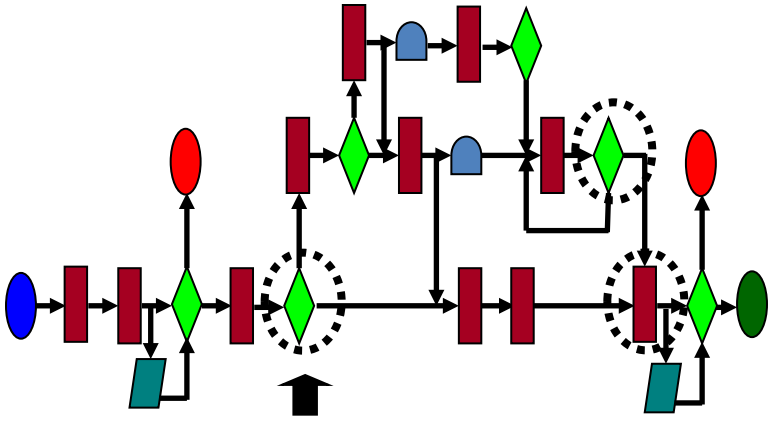
- Potency may be the most critical and laborious assay to develop and establish
- The FDA recommends developing an assay early and evaluating multiple potential measures of potency
- A potency assay must be in place by phase III and validated for licensure
- Should be guided by the underlying proposed mechanism of action and in vitro and pre-clinical proof of concept data
- A guidance document on potency is available: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM243392.pdf

Points to Consider Toward Validation of Potency Assay for Licensure

- What is the relevant biological or biochemical property of the product?
- Does selected property (CQA) correlate with biological activity of the product in vitro or in vivo?
- Is the test method fully validated?
  - Sensitive, accurate, robust and rugged
    - "Validation of Analytical Procedures" (ICH–Q2A), dated March 1995
    - "Validation of Analytical Procedures: Methodology (Q2B)," dated November 6, 1996,
    - "Validation of Analytical Procedures: Text and Methodology Q2(R1)" and was revised in November 2005.

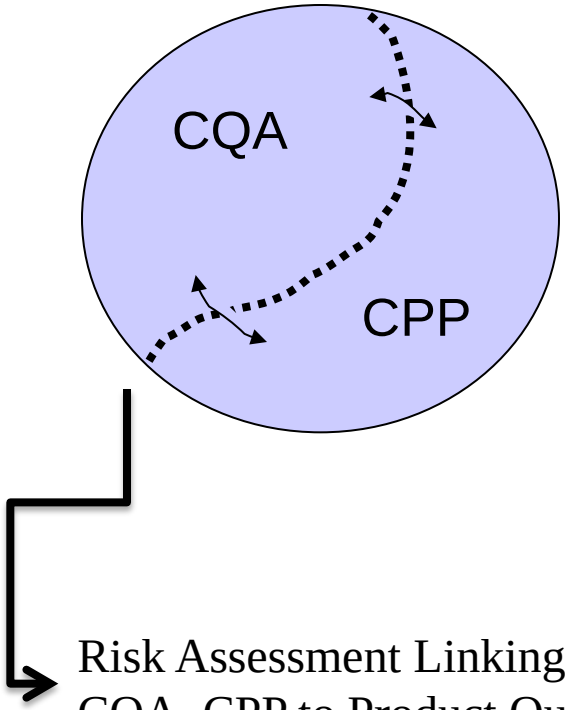
What are Critical Process Parameters?

- Critical Process Parameters (CPP) are independent process parameters most likely to affect the quality attributes of a product
- CPPs are determined by sound scientific research or manufacturing experience
- CPPs are controlled and monitored to confirm that the quality attributes of the product are maintained or improved



Risk Assessment

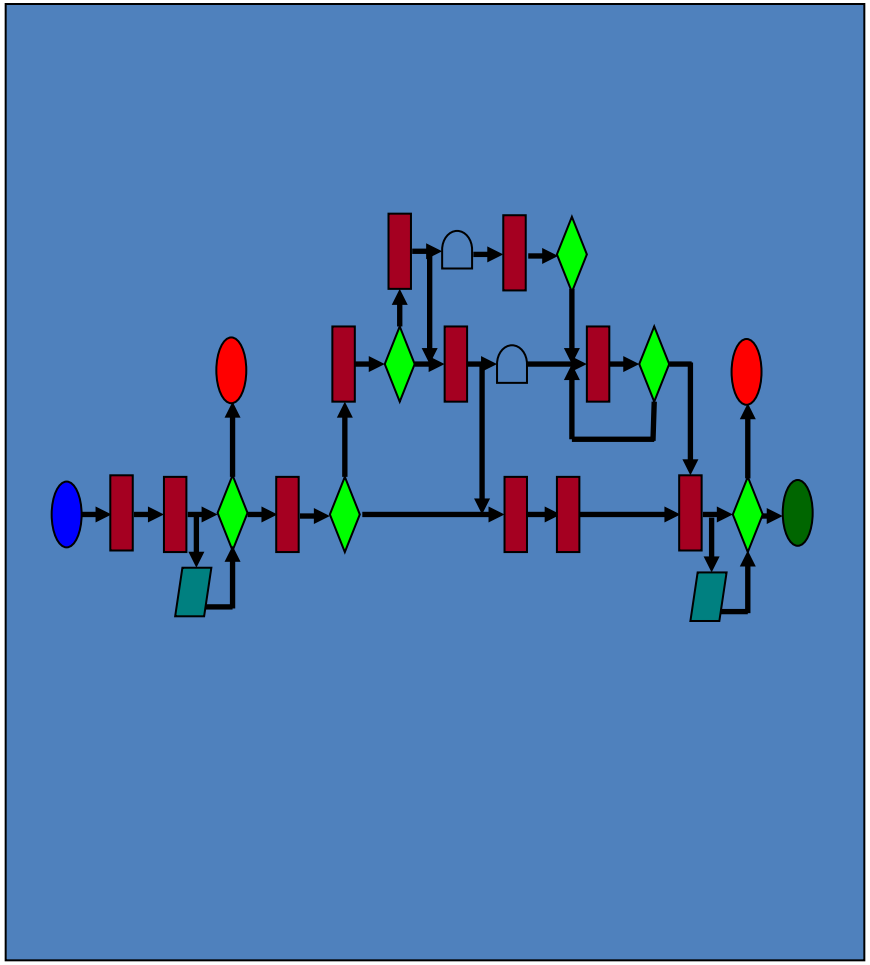
- Risk Assessment links Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) to the Drug Product Quality
  - Science Based
  - Performed early in Drug Development Cycle, repeated as more information becomes available
  - Robust Risk Assessment requires knowledge of CQA and CPP for a drug product
  - Risk Assessment tools used to identify and rank parameters with potential to impact product quality (ICH Q9)



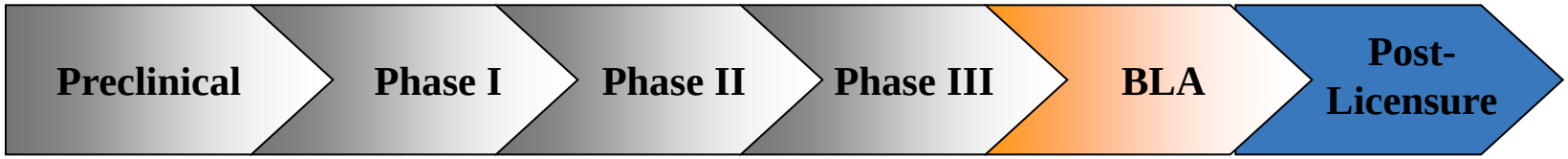
Risk Assessment Linking CQA, CPP to Product Quality

How to Deal with Process Change

- Process Changes (Examples)
  - Change of Manufacturing Step
  - Change of Starting Materials
  - Change of Reagents
  - Change of Vendors
  - Change of Cell Culturing Conditions
  - Change of Master Cell Bank
  - Scale Up or Scale out
  - Automation of the Process



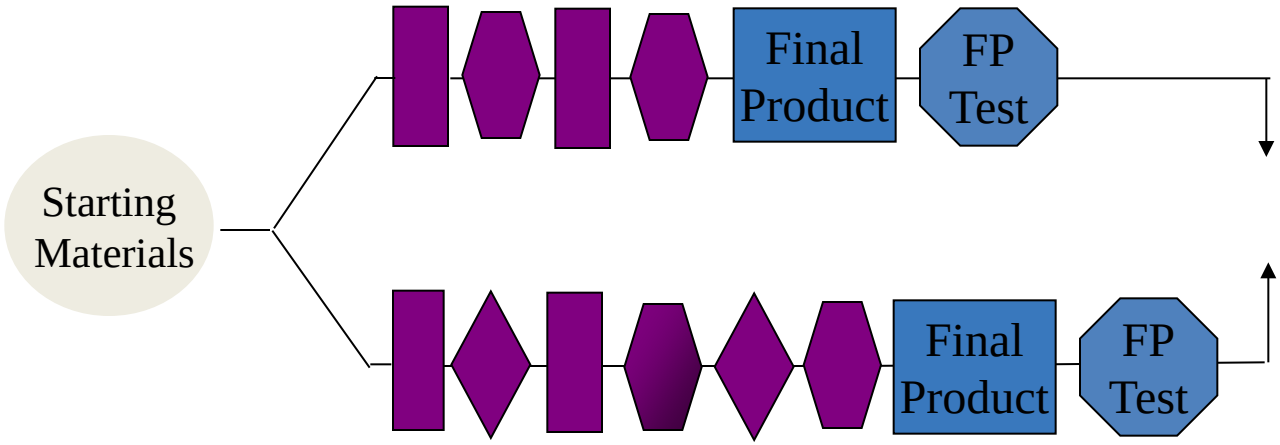
Introduction of Process Change into Product Lifecycle



- Process Change is Inevitable (not all of which is planned)
- Sponsor is Responsible to Plan for Change, Report and Implement Change, and Demonstrate Product Comparability
- Risk and Science Based

Process Change and Product Comparability

- Product comparability is intended to demonstrate that process changes do not adversely alter the relevant product's identity, purity, potency, and other physical characteristics (CQAs)



Comparability: A conclusion that products are highly similar before and after manufacturing process changes and that no adverse impact on the quality, safety, or efficacy of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might be indicated (ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process).

Tools for Establishing Comparability

- **Testing of the final product**
  - Tests Measuring Product Critical Quality Attributes
  - Other Relevant Assays

- **Manufacturing Yield**
  - Can be very helpful in demon-starting product comparability that is difficult to show by other means
  - Yields do not have to be high as long as they are consistent
  - Required by Regulation

- **Risk Management Plan**
  - Risk Assessment and Mitigation Plan

- **Comparability Protocol**

- **Process Validation**
  - 2011 Guidance for Industry Process Validation: General Principles and Practices

  Conveys FDA's current thinking on process validation and is consistent with basic principles first introduced in the 1987 guidance.

- **Quality by Design (QbD)**

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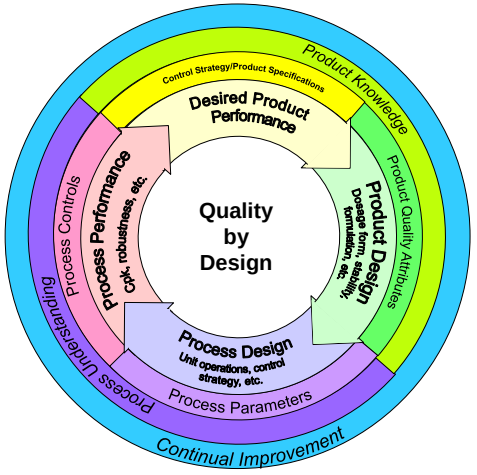


Establishing Comparability

- Major Considerations in Establishment of Comparability
  - What is the change?
  - What is the risk of impacting product quality?
  - Why the change is introduced?
  - ***When in the product lifecycle the proposed change is introduced?***

When in the Product Lifecycle the Proposed Change is Introduced (Risk Based Approach)

- For product with incomplete understanding of CQA overall risk associated with introducing major manufacturing changes increases substantially in late phases

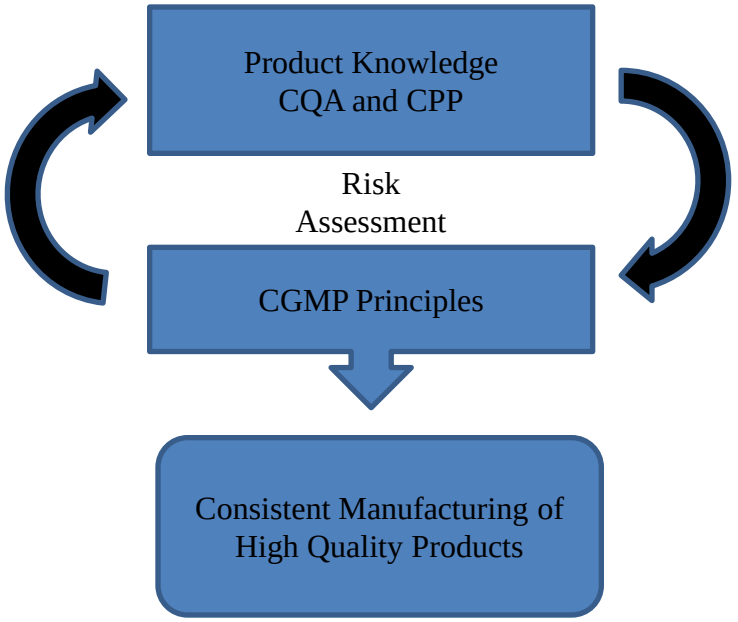
Examples	Risk (low)	Risk (Moderate)	Risk (High)	Risk Highest
Phase I	●			
Phase II	●	●		
Before Phase III or Pivotal Study		●	●	
During Phase III or Pivotal Study			●	●
During clinical study when combining clinical data before and after change is necessary			●	●
After Phase III or Pivotal Study and before Licensure				●
After Licensure				●

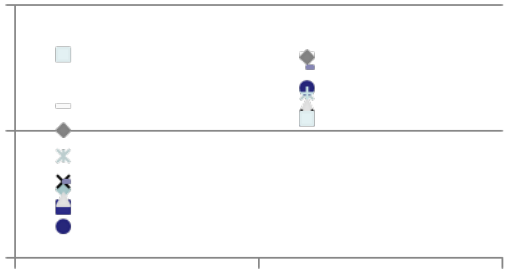
A few Points To Consider

- Knowledge of CQA is critical for establishing Product Comparability
- Establishing manufacturing control after process changes is critical
- Major manufacturing changes could require additional preclinical and clinical data
- Manufacturers are encouraged to make major changes prior to initiation of clinical studies conducted to demonstrate product efficacy
- **The more representative CQAs are of clinical safety and efficacy, the easier it is to evaluate the consequences of a manufacturing change**

Establishing Manufacturing Controls for Cell Therapy Products

- Understand Critical Quality Attributes for your product and Control Critical Process Parameters
- Conduct Full Risk Assessments
- Identify Sources of Process Variability
- Optimize and Re-evaluate Processes to Achieve Product Manufacturing Control and Consistency
- Apply CGMP Principles and Implement Process Change as Early as Possible





Relevant Guidance

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

CGMPs for Phase I Investigational Drugs

www.fda.gov/downloads/Drugs/.../Guidances/ucm070273.pdf

Potency Tests for Cellular and Gene Therapy Products

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM243392.pdf

Consideration for Early Phase Clinical Trials of Cellular and Gene Therapy Products

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM359073.pdf

Relevant Guidance

PDUFA V
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm

Process Validation: General Principles and Practices
http://www.fda.gov/downloads/Drugs/Guidances/UCM070336.pdf

Guidance for Industry Changes to an Approved Application: Biological Products:
www.fda.gov/downloads/BiologicsBloodVaccines/.../UCM170166.pdf

Guidance for Industry Comparability Protocols-Chemistry, Manufacturing, and Control Information
www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070545.pdf

FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products
www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm

Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074131.htm

Relevant Guidance

ICH Q5E – Includes concepts of comparability and how to establish comparability

ICH(http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf)

ICH Q8 – Pharmaceutical Development

Includes concepts of critical quality attributes and critical process parameters

Includes concepts of Quality by Design and examples of design space

www.fda.gov/downloads/Drugs/.../Guidances/ucm073507.pdf

ICH Q9 – Quality Risk Management

Describes a systematic process for the assessment, control, communication and review of quality risks

ICH Q10 – Pharmaceutical Quality Systems

Describes systems that facilitate establishment and maintenance of a state of control for process performance and product quality

OTAT Contact Information

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

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Phone: 240-402-7800

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Email: industry.biologics@fda.gov
Phone: (240) 402-8010

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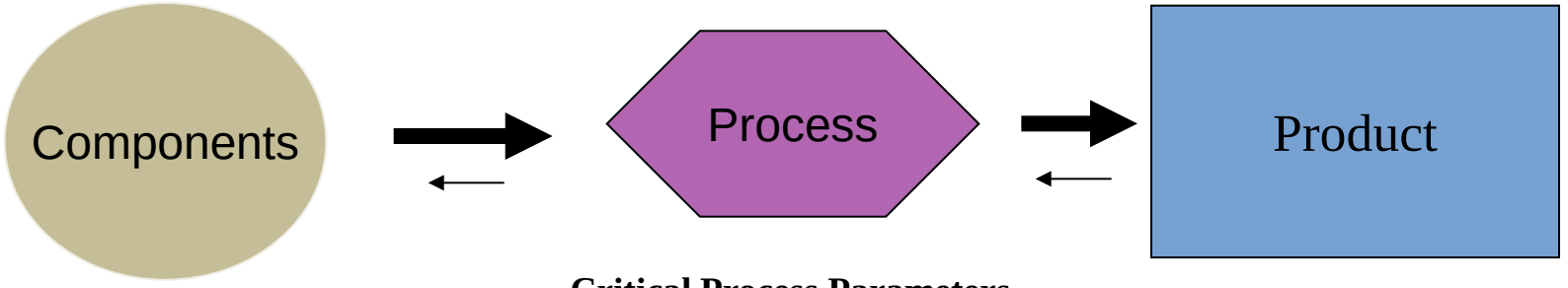
Round Table Discussion Items

- Control of Components
- Comparability Protocol

Control of Components



Qualification

Critical Process Parameters
Process Validation

Critical Quality Attributes
Release Specifications

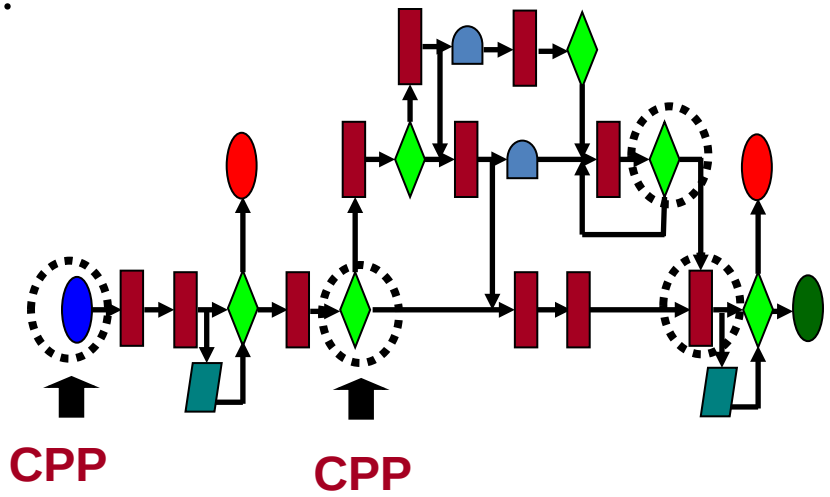
Control of Components

- **Component**- any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3)).

- **Components** include:
  - **Source Materials**
  - **Ancillary Materials/Reagents**
  - **Containers**

Control of Source Material

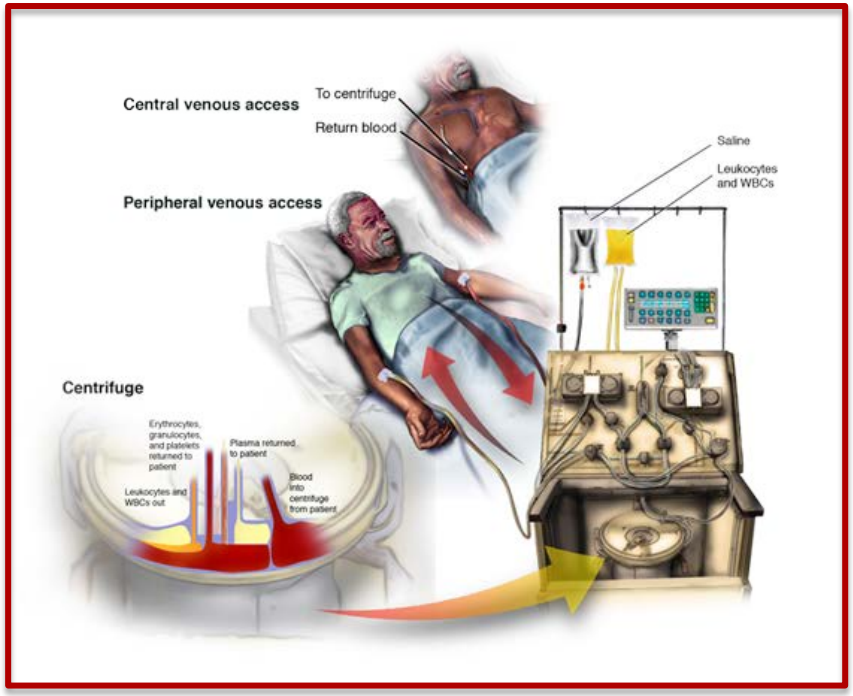
- **Biological Starting Material (also Source Material)** - Raw material from a biological source which is intended to be used in the fabrication of a drug and from which the active ingredient is derived either directly (e.g., PBMC, Leukapheresis, plasma derivatives, ascetic fluid, bovine lung, etc.) or indirectly (e.g., cell substrate, host/vector production cells, eggs, viral strains, etc.).



Guidance Document: Post – Notice of Compliance (NOC) Changes: Quality Document , September, 2009. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_quality_ac_sa_qualite-eng.php

Control of Source Material

- **Source Material**
  - **Apheresis products**
    - Apheresis machines are FDA cleared medical devices. Collection of PBMC is performed according to institutional SOPs and policies
  - **Identify and minimize sources of variability in collection, processing and shipment of Source Material**
  - **Identify and correlate quality and key attributes of Source Material to product quality**



Control of Critical Ancillary Material/Reagents

- **Ancillary Materials/Reagents** are components of the product which are intended to be used as a processing aid in the fabrication of the drug. Ancillary materials are commonly absent from the drug and may remain as an impurity in the drug at the end of the manufacturing process (e.g., biological additives used to supplement cell culture medium, cytokines, antibody etc.).

Control of Critical Ancillary Materials/Reagents

Ancillary Materials/Reagents:

- Encourage use of highest quality reagents available
  - FDA-approved or cleared, or clinical grade reagents
    - FDA does not approve or clear reagents for product manufacturing
  - Compendial reagents
  - CGMP grade-may be misleading
    - FDA does not verify the grade of reagents
  - Provide valid CoAs or qualification data
- As a manufacturer you are ultimately responsible to qualify the suitability of critical reagents used for product manufacturing

Control of Components with Direct Contact with the Final Product

- Containers for culturing flask, bags or other devices
  - Single Use Disposables
    - Extractables and Leachables (E&L)?
    - Container Integrity
- Containers for the Drug Substance storage
- **<u>Containers for Drug Product storage</u>**
  - E&L
  - Particulates
  - Sampling
  - Container Closure Integrity Test

Comparability Protocol (CP)

- What is a Comparability Protocol (CP)
- How it is used
- What it should contain

What is a CP

A CP is a written plan for assessing the effect of a proposed change(s) on the product quality

How it is used

- Licensed Products:
  - Approved CP allows manufacturers to implement major change(s) as agreed upon.
  - Approved CP supports a reduced reporting category.
- Investigational Products:
  - CP may be required for implementing major manufacturing changes during late phase-clinical trials.

What it Should Contain

- A description of the proposed change(s)
- A rationale for the proposed change(s)
- Comparability study design for the proposed change(s)
  - Comparative assessment of Quality Attributes before and after change (side-by-side comparison is preferred)
  - Justification for well defined acceptance criteria for establishing comparability
  - Detailed analytical procedures, sampling plan, statistical methods and analysis
  - Reporting commitment
- Risk Assessment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