Characterization and Quality Control of Biological Products

Raymond D. Harris, PhD
Biological Resources Branch
Developmental Therapeutics Program, DCTD, NCI

NIH NATIONAL CANCER INSTITUTE

DTP Drug Development Workshop
Session V – Development of Biological Products
September 10, 2021

Introduction and Outline

- Quality Control Definition
- Critical Quality Attributes
- QC Components
- Common Pitfalls
- Resources

What is Quality Control

Quality System Component

Function to generate **laboratory data** demonstrating that your Drug Product has been manufactured in compliance with GMP.

Includes testing of:

- utility & EM samples
- raw materials
- in-process samples
- Drug Substance (DS)
- Drug Product (DP)

Tests must be suitable and capable of ensuring DS & DP Critical Quality Attributes.

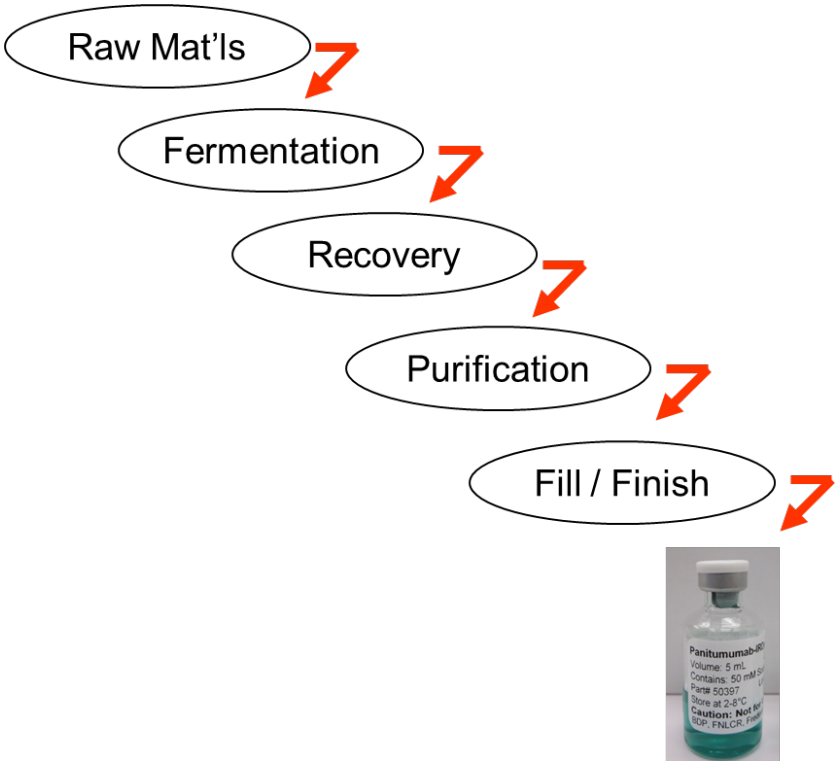
Critical Quality Attributes

- CQA's are physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- CQA's demonstrate SISQP

Safety	Does no harm
Identity	Is what it's supposed to be
Strength	Sufficiently potent
Quality	Meets specified requirements
Purity	Free of contamination

- CQA's established in Target Product Profile (TPP)

Manufacturing Process

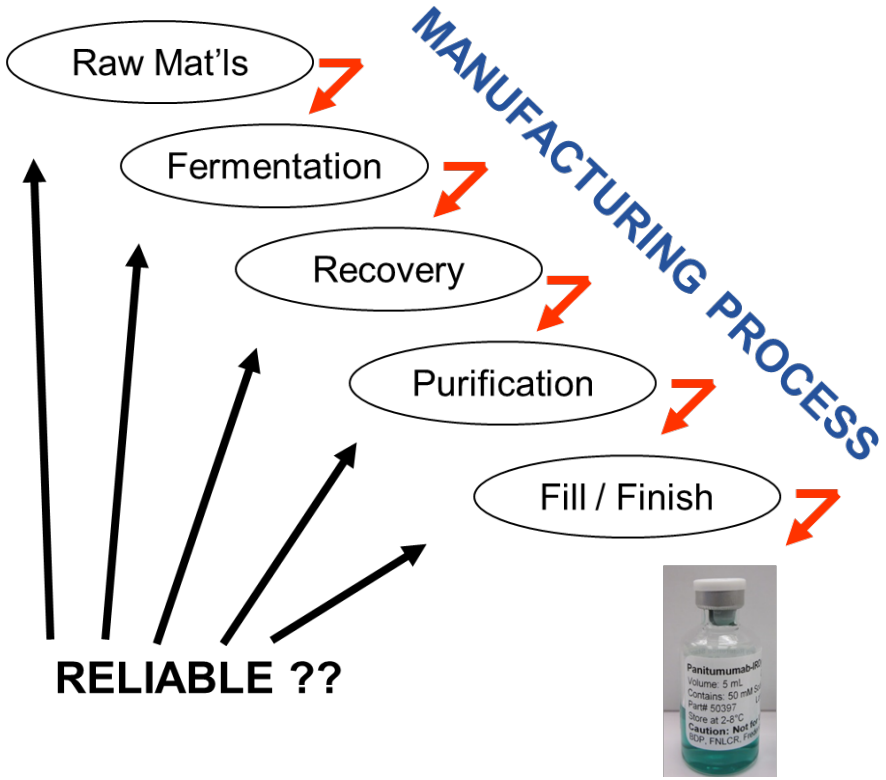


Product Meet specifications?

Meet Specs?

Answer with Laboratory Data

Reliability of the Manufacturing Process



Harvest

In process

Drug Substance

Drug Product

Meet Specs?

Answer with Laboratory Data

Laboratory Data

- Used to establish whether the product meets specifications
- Used to establish whether the subprocesses are reliable

"Testing lies at the heart of a drug manufacturer's successful operation. Through testing, companies validate their processes and ensure the quality of batches for release."

(United States vs. Barr Laboratories)

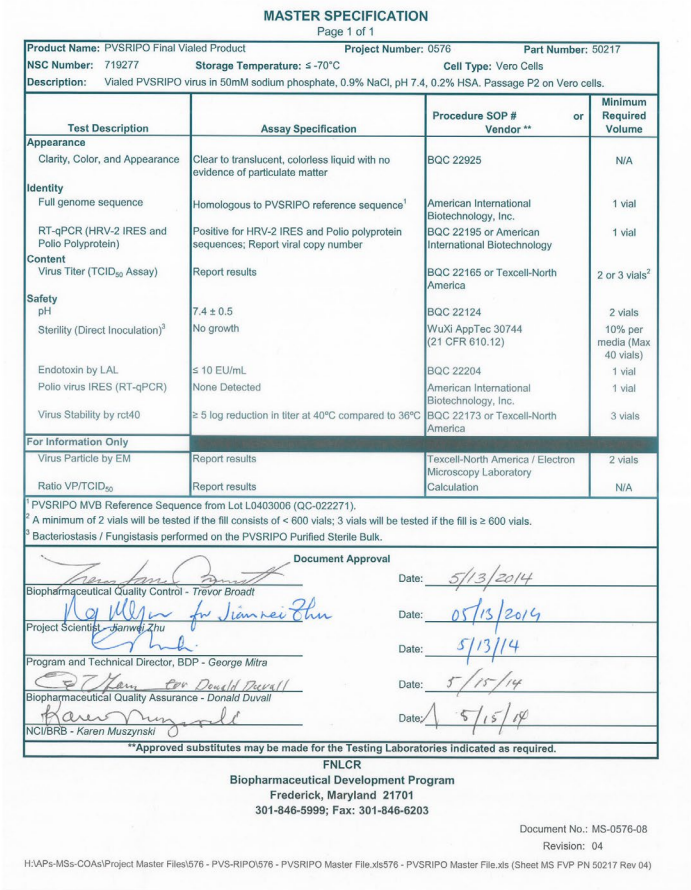
Key Considerations

- Manufacturing GMP products needs to be CONSISTENT so that each vial represents all the vials in the lot.
- When doing testing, need to ensure the validity and credibility of the testing are maximized.
- How do we know laboratory data are reliable?

General Testing Requirements

- Establish written specifications, standards, sampling plans, procedures (including changes)
  - Must be scientifically sound, suitable and reliable
  - Include a description of sampling and testing procedures
- Document activities at the time they are performed
- Deviations must be recorded and justified
- Determine conformance to established specifications
- Test samples must be representative and identified
- Use equipment calibrated at suitable intervals per written program
- Maintain suitable sample retains

Master Specification



MASTER SPECIFICATION

Page 1 of 1

Product Name: PVSRIPO Final Vialed Product **Project Number:** 0576 **Part Number:** 50217

NSC Number: 719277 **Storage Temperature:** ≤ -70°C **Cell Type:** Vero Cells

Description: Vialed PVSRIPO virus in 50mM sodium phosphate, 0.9% NaCl, pH 7.4, 0.2% HSA. Passage P2 on Vero cells.

Test Description	Assay Specification	Procedure SOP # or Vendor **	Minimum Required Volume
Appearance			
Clarity, Color, and Appearance	Clear to translucent, colorless liquid with no evidence of particulate matter	BQC 22925	N/A
Identity			
Full genome sequence	Homologous to PVSRIPO reference sequence[1]	American International Biotechnology, Inc.	1 vial
RT-qPCR (HRV-2 IRES and Polio Polyprotein)	Positive for HRV-2 IRES and Polio polyprotein sequences; Report viral copy number	BQC 22195 or American International Biotechnology	1 vial
Content			
Virus Titer ($TCID_{50}$ Assay)	Report results	BQC 22165 or Texcell-North America	2 or 3 vials[2]
Safety			
pH	7.4 ± 0.5	BQC 22124	2 vials
Sterility (Direct Inoculation)[3]	No growth	WuXi AppTec 30744 (21 CFR 610.12)	10% per media (Max 40 vials)
Endotoxin by LAL	≤ 10 EU/mL	BQC 22204	1 vial
Polio virus IRES (RT-qPCR)	None Detected	American International Biotechnology, Inc.	1 vial
Virus Stability by rct40	≥ 5 log reduction in titer at 40°C compared to 36°C	BQC 22173 or Texcell-North America	3 vials
For Information Only			
Virus Particle by EM	Report results	Texcell-North America / Electron Microscopy Laboratory	2 vials
Ratio VP/$TCID_{50}$	Report results	Calculation	N/A

[1] PVSRIPO MVB Reference Sequence from Lot L0403006 (QC-022271).

[2] A minimum of 2 vials will be tested if the fill consists of < 600 vials; 3 vials will be tested if the fill is ≥ 600 vials.

[3] Bacteriostasis / Fungistasis performed on the PVSRIPO Purified Sterile Bulk.

Document Approval

Biopharmaceutical Quality Control - *Trevor Broadt* Date: 5/13/2014

Project Scientist - *Jianwei Zhu* Date: 05/13/2014

Program and Technical Director, BDP - *George Mitra* Date: 5/13/14

Biopharmaceutical Quality Assurance - *Donald Duvall* Date: 5/15/14

NCI/BRB - *Karen Muszynski* Date: 5/15/14

****Approved substitutes may be made for the Testing Laboratories indicated as required.**

FNLCR

Biopharmaceutical Development Program

Frederick, Maryland 21701

301-846-5999; Fax: 301-846-6203

Document No.: MS-0576-08

Revision: 04

H:\APs-MSs-COAs\Project Master Files\576 - PVS-RIPO\576 - PVSRIPO Master File.xls576 - PVSRIPO Master File.xls (Sheet MS FVP PN 50217 Rev 04)

Acceptance criteria

- Test dependent
  - Safety tests could have limits established by Regulatory Authorities (e.g. sterility, endotoxin)
  - Industry established limits, such as level of purity for a protein or mAb product.
- Established based on data and scientific analysis obtained during process development
  - Cell-based assays have high level of variability
- Data are limited in early development
  - Report results discouraged
  - % of standard, wide range

Assay Validation and Qualification

- Validation confirms assay capabilities: method studied is well-defined, specific assay capabilities have pre-defined acceptance criteria included in validation protocol.
- Validation usually not required at the initial stages of drug development.
- Qualified assay: well-controlled
  - Measures method performance capabilities
  - Demonstrates suitability for intended purpose and is reproducible
    - Standards, positive and negative controls

Product release

- Cumulative review of manufacturing records and other relevant information
  - Procedures were followed
  - Product tests were performed appropriately
  - Acceptance criteria were met
- Unexpected results (also referred to as OOS, OOT) must be investigated

Investigation of Unexpected Results

- Unexpected result cannot be discarded or dismissed (no testing into compliance)
- US vs Barr Laboratories: FDA issued Guidance (2006)
- Establish and follow a written procedure
  - Investigation concludes a test error was performed; result is invalid
  - Investigation concludes no test error was performed; result is valid indicates production error
    - Execution error
    - Process error
- Valid results failing to meet specifications ⟶ batch rejection

Example Certificate of Analysis

CERTIFICATE OF ANALYSIS

Page 1 of 2

Product Name: PVSRIPO Final Vialed Product **Project Number:** 0576 **Part Number:** 50217

NSC Number: 719277 **Production Date:** 5/28/2014 **Lot Number:** L1402001 **Lot Size:** 1766 vials

Container Size/Fill Volume: 2mL glass / 0.5mL **Storage Temperature:** ≤-70°C

Description: Vialed PVSRIPO virus in 50 mM sodium phosphate, 0.9% NaCl, pH 7.4, 0.2% HSA. Passage P2 on Vero Cell Lot #217002-2.

Test Description	Assay Specification	Test SOP # or Study #	QC Test Request Number	Result
Appearance				
Clarity, Color, and Appearance	Clear to translucent, colorless liquid with no evidence of particulate matter	BQC 22925	QC-053194	Clear to translucent, colorless liquid with no evidence of particulate matter
Identity				
Full genome sequence	Homologous to PVSRIPO reference sequence[1]	American International Biotechnology, Inc., Study #LEIDOS-092314TB	QC-053193	Homologous to PVSRIPO reference sequence[1]
RT-qPCR (HRV-2 IRES and Polio Polyprotein)	Positive for HRV-2 IRES and Polio Polyprotein sequences; Report viral copy number	American International Biotechnology, Inc., Study #LEIDOS-080114TB	QC-053195	Positive for HRV-2 IRES and Polio Polyprotein sequences; 1.58×10^{12} viral copies/mL
Content				
Virus Titer ($TCID_{50}$ Assay)	Report results	Texcell North America, Study #14-81-550-2	QC-053192	4.48×10^{9} $TCID_{50}$/mL
Safety				
pH	7.4 ± 0.5	BQC 22124	QC-053196	7.2
Sterility (Direct inoculation)	No growth	WuXi AppTec 30744, (21 CFR 610.12)	QC-053197	No growth
Polio virus IRES (RT-qPCR)	None Detected	American International Biotechnology, Inc., Study #LEIDOS-080114TB	QC-053198	None Detected; < 100 wild-type Polio genomic copies per 2.6×10^{7} copies of PVSRIPO
Virus Stability by rct40	≥ 5 log reduction in titer at 40ºC from 36ºC	Texcell North America, Study #14-85-562-2	QC-053199	> 7.09 log reduction in titer at 40ºC from 36ºC
Endotoxin by LAL	≤ 10 EU/mL	BQC 22204	QC-053191	< 0.5 EU/mL
For Information Only				
Virus Particle by EM	Report results	Texcell North America, Study #14-80-521.5-2; FNLCR Electron Microscopy Laboratory	QC-053200	7.0×10^{10} vp/mL
Ratio VP/$TCID_{50}$	Report results	Calculation	N/A	15.6

H:\BRB Shared Docs\PVSRIPO\576 PVSRIPO HP-Bulk-FVP.xlsx (Sheet - COA-PVSRIPO FVP L1402001)

Stability

- FDA ‘recommend [=require] initiation of a stability study using representative samples of the phase 1 investigational drug to monitor the stability and quality of the phase 1 investigational drug during the clinical trial’
- Subset of Drug Product release tests performed that are stability indicating assays
- Establish Stability Program that follows Regulatory Guidance documents
- Conducting stability on engineering batch(es) can help speed IND submission without compromising Product Quality

Common Pitfalls

- Consider product characterization in early stages of development
  - Tests will be needed as process development is performed in addition to demonstrating product quality
  - Function of biological product worthy of particular focus
- Establish suitable standards and document changes along with rationale as development proceeds
- Establish MS early in development
- Specifications are expected to tighten as product development proceeds

Common Pitfalls II

- Ensure adequate samples are taken for in-process & product testing including retains
  - Include Bill of Testing in BR
- DS/DP test results should be scientifically sound (e.g. purity of DP shouldn't be >> DS)
- Product testing alone is insufficient to demonstrate controlled manufacture of product in compliance with appropriate GMPs
- Seek early feedback from FDA on adequacy of proposed MS for DS, DP, and Stability Program
  - Present plans in FDA submission and ask for their agreement (they'll tell you if they don't!) don't ask FDA to tell you what testing should be done.

Resources

- ICH Guidance Q8 (R2) Pharmaceutical Development
- ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products
- FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs
- FDA Guidance: Analytical Procedures and Methods Validation for Drugs & Biologics
- FDA Guidance: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products

Resources II

- FDA Guidance: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production
- ICH Guidance Q1A: Stability Testing of New Drug Substances & Products
- ICH Guidance Q1E: Evaluation of Stability Data
- ICH Guidance Q5C: Stability Testing of Biotechnological & Biological Products