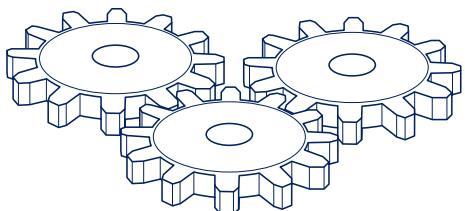


Technical Report No. 60

Process Validation: A Lifecycle Approach

PCMOSM
Paradigm Change in
Manufacturing OperationsSM



2013



PDA Task Force on Technical Report No. 60: Process Validation: A Lifecycle Approach

Authors

Scott Bozzone, Ph.D., Chair, Pfizer, Inc.

Harold S. Baseman, Co-Chair, Valsource, LLC

Vincent Anicetti, Parenteral Drug Association, Keck Graduate Institute

John A. Bennan, Ph.D., ComplianceNet, Inc.

Michael N. Blackton, Imclone Systems, Inc.

Vijay Chiruvolu, Ph.D., MBA, Amgen, Inc.

Rebecca A. Devine, Ph.D., Consultant to the Biopharmaceutical Industry

Stephen Duffy, Covidien, LLC

Panna L. Dutta, Ph.D., The Medicines Company

Kurtis Epp, BioTechLogic, Inc.

Igor Gorsky, Shire Pharmaceuticals, Inc.

Norbert Hentschel, Boehringer Ingelheim Pharma GmbH & Co., KG

Pedro Hernandez, Ph.D., PHPD, LLC

Irwin Hirsh, Novo Nordisk A/S

Raj Jani, Baxter Healthcare Corporation

Peter F. Levy, PL Consulting, LLC

Michael Long, PhD Concordia Valsource, LLC

John McShane, Roche-Genentech, Inc.

Victor G. Maqueda, Sr., Consultant

José Luis Ortega, Pharma Mar S.A. Sociedad Unipersonal

Elizabeth Plaza, Pharma-Bio Serv, Inc.

Praveen Prasanna, Ph.D., Shire Human Genetic Therapies, Inc.

David Reifsnyder, Roche-Genentech, Inc.

Markus Schneider, Ph.D., Novartis Pharma AG

Iolanda Teodor, Baxter Healthcare Corporation

Mark Varney, Abbott Laboratories

Alpaslan Yaman, Ph.D., Biotech, Pharma and Device Consulting, LLC

Wendy Zwolenski-Lambert, Abbott Laboratories

This technical report was developed as part of PDA's Paradigm Change in Manufacturing Operations (PCMO) project. The content and views expressed in this Technical Report are the result of a consensus achieved by the members of the authorizing Task Force, and are not necessarily the views of the organizations they represent.

Process Validation: A Lifecycle Approach

Technical Report No. 60

ISBN: 978-0-939459-51-3

© 2013 Parenteral Drug Association, Inc.

All rights reserved.



Paradigm Change in Manufacturing Operations (PCMOSM)

PDA launched the project activities related to the PCMOSM program in December 2008 to help implement the scientific application of the ICH Q8, Q9 and Q10 series. The PDA Board of Directors approved this program in cooperation with the Regulatory Affairs and Quality Advisory Board, and the Biotechnology Advisory Board and Science Advisory Board of PDA.

Although there are a number of acceptable pathways to address this concept, the PCMO program follows and covers the drug product lifecycle, employing the strategic theme of process robustness within the framework of the manufacturing operations. This project focuses on Pharmaceutical Quality Systems as an enabler of Quality Risk Management and Knowledge Management.

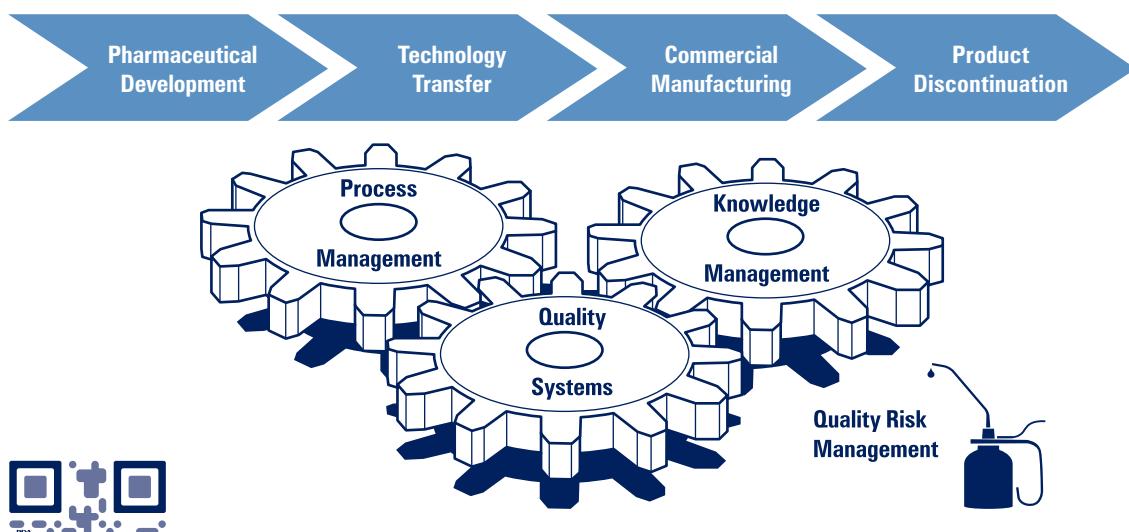
Using the Parenteral Drug Association's (PDA) membership expertise, the goal of the Paradigm Change in Manufacturing Operations Project is to drive the establishment of 'best practice' documents and /or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products (IMPs) and commercial products in implementing the ICH guidelines on Pharmaceutical Development (ICH Q8, Q11), Quality Risk Management (ICH Q9) and Pharmaceutical Quality Systems (ICH Q10).

The PCMO program facilitates communication among the experts from industry, university and regulators as well as experts from the respective ICH Expert Working Groups and Implementation Working Group. PCMO task force members also contribute to PDA conferences and workshops on the subject.

PCMO follows the product lifecycle concept and has the following strategic intent:

- Enable an innovative environment for continual improvement of products and systems
- Integrate science and technology into manufacturing practice
- Enhance manufacturing process robustness, risk based decision making and knowledge management
- Foster communication among industry and regulatory authorities

The Product Lifecycle



For more information, including the PCMOSM Dossier, and to get involved, go to www.pda.org/pcmo

Table of Contents

1.0 INTRODUCTION	1
1.1 Purpose and Scope.....	1
1.2 Background	1
2.0 GLOSSARY OF TERMS	6
2.1 Acronyms	9
3.0 BUILDING AND CAPTURING PROCESS KNOWLEDGE (STAGE 1 — PROCESS DESIGN) 10	
3.1 Deliverables from Stage 1	
Process Validation	12
3.2 Quality Target Product Profile (QTPP).....	12
3.3 Critical Quality Attributes.....	13
3.4 Define the Manufacturing Process	14
3.5 Analytical Methods.....	20
3.6 Risk Assessment and Parameter Criticality Designation.....	20
3.7 Process Characterization	23
3.8 Product Characterization Testing Plan.....	23
3.9 Control Strategy.....	24
3.10 Clinical Manufacturing Experience – Batch Records and Production Data.....	25
3.11 Process Design Report.....	26
3.12 Process Validation Master Plan	26
3.13 Stage 1 Manufacturing and Technology Considerations.....	26
4.0 PROCESS QUALIFICATION (STAGE 2)	28
4.1 Strategies for System Design and Qualification.....	28
4.1.1 Engineering and Design	29
4.1.1.1 Risk Assessment.....	29
4.1.2 Installation.....	29
4.1.3 Qualification Plan	29
4.1.3.1 Test Functions and Acceptance Criteria.....	30
4.1.4 Maintaining Systems in a State of Control	30
4.2 Process Performance Qualification	31
4.2.1 PPQ Readiness	31
4.3 Design Strategy for Process Performance Qualification (PPQ).....	33
4.3.1 Use of Prior Knowledge and Stage 1 Data to Support PPQ.....	33
4.3.2 PPQ Study Design	34
4.3.2.1 Number of Batches.....	35
4.3.2.2 PPQ at Normal Operating Conditions ..	35
4.3.2.3 PPQ Using Individual Unit Operation Studies	36
4.3.2.4 PPQ Using Bracketing, Matrix, and Family Approaches	36
4.3.2.5 Bracketing Approach.....	36
4.3.2.6 Matrix Approach	36
4.3.2.7 Family (Grouping) Approach	37
4.3.2.8 Process Analytical Technology	38
4.3.2.9 Sampling Strategy	39
4.3.2.10 Setting PPQ Acceptance Criteria....	39
4.4 PPQ Protocol	40
4.5 PPQ Report	42
4.6 Transition to Continued Process Verification 43	
5.0 CONTINUED PROCESS VERIFICATION (STAGE 3)	44
5.1 Establishing a Monitoring Program	44
5.1.1 Purpose and Strategy	44
5.1.2 Documenting the CPV Program	44
5.1.3 Legacy Products and Continued Process Verification.....	46
5.1.4 Demonstrating Continued Process Verification.....	47
5.1.5 CPV Monitoring Plan.....	48
5.1.6 Data Analysis and Trending	48
5.2 Incorporation of Feedback from CPV Monitoring.....	49
5.2.1 Quality Systems and CPV	49
5.3 CPV Data Review and Reporting	50
6.0 PROCESS VALIDATION ENABLING SYSTEMS AND TECHNOLOGY	51
6.1 Application of Risk Management	51
6.1.1 Risk Management in Stage 1 – Process Design	52
6.1.2 Risk Management in Stage 2 – Process Qualification	53
6.1.3 Risk Management in Stage 3 – Continued Process Verification	54
6.1.4 Raw Material Risk Management Considerations	54
6.2 Statistical Analysis Tools	55
6.2.1 Design of Experiments (DoE)	57
6.2.2 Statistical Process Control and Process Capability.....	59
6.2.2.1 Statistical Process Control Charts	60
6.2.2.1.1 Factors to Consider in Designing a Control Chart.....	62
6.2.2.1.2 Types of Control Charts	62
6.2.2.1.3 Process Capability.....	62
6.2.3 Statistical Acceptance Sampling	64

6.2.4	Number of Lots for Stage 2 Process Performance Qualification (PPQ).....	66
6.3	Process Analytical Technology (PAT)	66
6.3.1	Selection of PAT System.....	67
6.3.2	Process Validation Considerations During the PAT System Design Stage	69
6.3.2.1	Risk Assessment.....	69
6.3.2.2	In-Process Application and Method Development	69
6.3.3	Process Qualification Considerations for PAT.....	69
6.3.4	Continued Process Verification Considerations for PAT.....	70
6.4	Technology Transfer	70
6.5	Knowledge Management.....	73
7.0	EXAMPLES	75
7.1	Large Molecule (Biotech).....	75
7.2	Small Molecule (Parenteral).....	77
8.0	APPENDICES.....	81
8.1	Appendix 1: Statistical Methods for Determining the Number of Lots.....	81
8.1.1	Average Run Length (ARL) to detect a $p \times 100\%$ lot failure rate.....	81
8.1.3	Within and Between Lot Normal Tolerance Intervals.....	82
8.1.4	Statistical Process Control Charts	82
8.1.5	P_{pk} , C_{pk} Process Capability Metrics.....	83
8.1.6	Assure the Lot Conformance Rate is Above an Acceptable Rate With Specified Confidence.....	84
8.1.7	Wald Sequential Probability Ratio	84
8.1.8	Narrow Limit Gauging	85
8.1.9	Demonstrate Between-Lot Variation is Less Than Within-Lot Variation (Anova)	85
8.1.10	Sample Size	86
8.1.11	Demonstrate the Between-Lot Standard Deviation $\sigma_b \leq$ Acceptable Value X	86
8.1.12	Demonstrating equivalence between lots	86
8.2	Appendix 2: Types of Control Charts.....	87
8.2.1	Control Charts for Variables Data.....	87
8.2.2	Control Charts for Attributes Data.....	88
8.2.3	Performance of Control Charts: Average Run Length (ARL)	88
9.0	REFERENCES.....	89