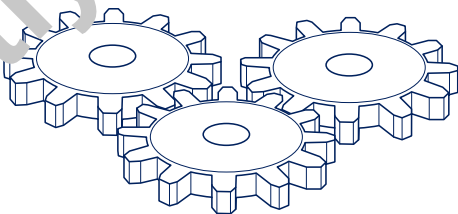


Technical Report No. 60

Process Validation:

A Lifecycle Approach

PCMO
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 Reifsnnyder, 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 Zvolewski-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

ISPN: 978-0-939459-51-3

© 2012 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.

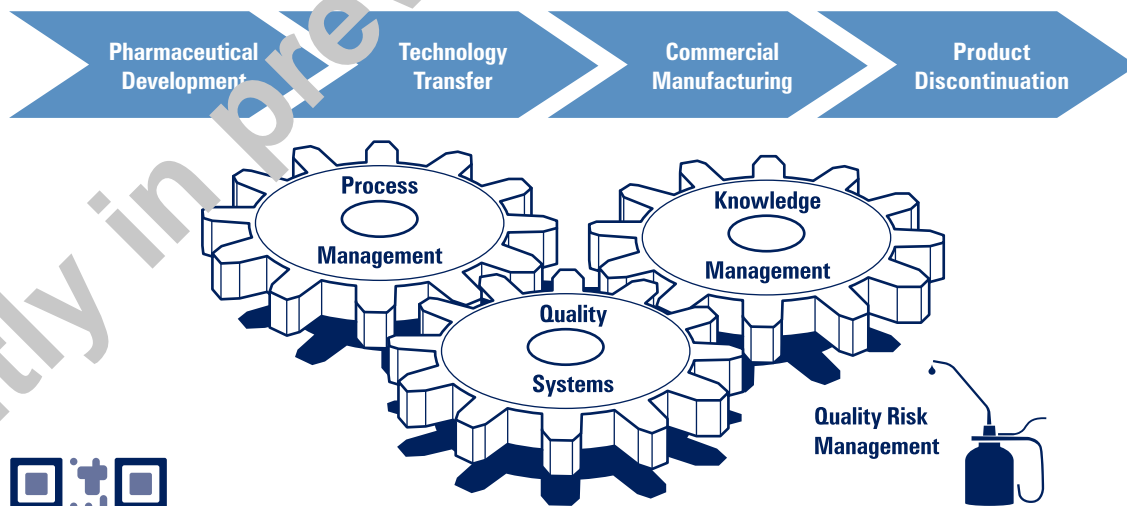
Using the Parenteral Drug Association's (PDA) membership expertise, the goal of the Paradigm Change in Manufacturing Operations Project is to drive the establishment of 'best practice' documents and /or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products (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 |

FIGURES AND TABLES INDEX

| | | | | | |
|------------------------|---|----|---------------------------|---|----|
| Figure 1.2-1 | Applicability of ICH Q8 (R2) through Q11 Relative to the FDA Stage Approach to Process Validation | 3 | Figure 6.2.2-1 | Process in Classical Statistical Control; Common Cause Variation only | 59 |
| Figure 1.2-2 | Common Timing of Process Validation Enablers and Deliverables to Validation Stage Activities | 5 | Figure 6.2.2-2 | Process Not in Statistical Control -Special Cause Variation..... | 60 |
| Figure 3.0-1 | Overall Sequence of Process Validation Activities | 11 | Figure 6.2.2-3 | A Process with Both Within-lot and Between-lot Variation | 60 |
| Figure 3.4-1 | Example Process Diagram for a Tangential Flow Filtration Step | 15 | Figure 6.2.2.1-1 | Xbar/S Control Chart for Fill Weight, n=5 per group | 61 |
| Table 3.4-1 | Example Process Parameter Table for a Tangential Flow Filtration Step .. | 16 | Figure 6.2.2.1.3-1 | Process Capability Statistics C_p and C_{pk} | 63 |
| Figure 3.6-1 | Decision Tree for Designating Parameter Criticality | 22 | Figure 6.2.2.1.3-2 | Examples of Process Capability Statistics C_p and C_{pk} | 63 |
| Figure 4.1-1 | Typical System Qualification Sequence.. | 28 | Table 6.2.2.1.3-2 | Relationship Between Capability and % of Per Million Nonconforming ... | 64 |
| Table 4.1.3-1 | Qualification Information..... | 30 | Figure 6.2.3-1 | Example of an Operating Characteristic Curve | 65 |
| Figure 4.3.1-1 | Relationship of Prior Knowledge to the Amount of PPQ Data Required..... | 33 | Table 6.3.1-1 | Examples of PAT Tools and Their Application | 68 |
| Table 4.3.2.6-1 | Illustration of a Matrix Approach for Filling Process PPQ..... | 37 | Table 6.4-1 | Technology Transfer Activities Throughout Product Lifecycle | 71 |
| Table 4.4-1 | Example of PPQ Acceptance Criteria Table..... | 42 | Figure 6.4-1 | Distribution of Technology Transfer Activities throughout the Product Lifecycle | 73 |
| Figure 5.1.2-1 | Development of a Continued Process Verification Plan..... | 45 | Table 7.1-1 | Stage 1: Process Design..... | 75 |
| Figure 5.1.2-2 | CPV Plan within Validation Documentation System | 45 | Table 7.1-2 | Stage 2: Process Qualification (Continued)..... | 76 |
| Figure 5.1.3-1 | CPV Plan Determination for Legacy Product | 47 | Table 7.1-3 | Stage 3: Continued Process Verification..... | 77 |
| Figure 5.2.1-1 | Body of Knowledge and Maintenance of Process Control | 49 | Table 7.2-1 | Stage 1: Process Design..... | 77 |
| Figure 6.1-1 | Quality Risk Management: A Lifecycle Tool for Process Development and Validation..... | 52 | Table 7.2-2 | Stage 2: Process Qualification | 79 |
| Figure 6.1.2-1 | Product Attribute Criticality Risk Assessment Example | 53 | Table 7.2-3 | Stage 3: Continued Process Verification... .. | 80 |
| Table 6.1.1 | Risk-Based Qualification Planning..... | 53 | Table 8.1.2-1 | Expected Between-Lot Variation Coverage in n_L Lots..... | 81 |
| Table 6.1.2 | Severity Rating and Sampling Requirements | 54 | Table 8.1.6-1 | Number of lots to demonstrate confidence for lot conformance rate .. | 84 |
| Table 6.2-1 | Statistical Methods and the Typical Stages at Which They Are Used | 56 | Figure 8.1.7-1 | Wald's Sequential Probability Ratio Example..... | 85 |
| | | | Table 8.1.9-1 | Effect of between-lot variation on the total process variance | 85 |
| | | | Table 8.1.10-1 | Sample Size to estimate a standard deviation to within $\pm X\%$ of true value | 86 |

Currently in preview, click buy full version

1.0 Introduction

1.1 Purpose and Scope

This Technical Report (TR) is intended to provide practical guidance on the implementation of a lifecycle approach to pharmaceutical process validation (PV). It contains information that enables manufacturers to implement globally-compliant PV programs consistent with the principles of recent lifecycle-based PV guidance documents and current expectations for Pharmaceutical Quality Systems (1-4). In pharmaceutical manufacturing, “process validation” is the collection and evaluation of data -from the process design stage through commercial production that establishes scientific evidence that a process is capable of consistently delivering quality product (3). The U.S. FDA and EMA consider PV a requirement in both general and specific terms in current Good Manufacturing Practice (cGMP) guidelines and an essential element in the assurance of drug quality (2,3,5).

The PV lifecycle concept links product and process development, the qualification of the commercial manufacturing processes, and maintenance of the commercial production process in a coordinated effort (3). When based on sound process understanding and used with quality risk management principles, the lifecycle approach allows manufacturers to use continuous process verification (enhanced approach) in addition to, or instead of, traditional PV (1,2,6).

The information in this TR applies to the manufacturing processes for drug substances and drug products, including:

- Pharmaceuticals, sterile and non-sterile
- Biotechnological/biological products, including vaccines
- Active Pharmaceutical Ingredients (APIs)
- Radiopharmaceuticals
- Veterinary drugs
- Drug constituents of combination products (e.g. a combination drug and medical device)

This report is prepared for global use and applies to new and existing (i.e., legacy) commercial manufacturing processes. Its scope does not include manufacturing processes for:

- Medical devices
- Dietary supplements
- Medicated feed
- Human tissues

Although these product categories are outside the scope of this TR, its recommendations are based on modern quality concepts, ICH Quality Guidelines, and recent regulatory authority guidance documents. As such, it may be a useful reference in the development of PV lifecycle approaches for other product categories. The validation of ancillary supporting operations used in pharmaceutical manufacturing processes is not discussed in the report. Many PDA TRs already provide specific guidance for such procedures; for example, cleaning, aseptic process simulation, moist heat sterilization and dry heat sterilization (7-10).

1.2 Background

The lifecycle concept includes all phases in the life of a product from initial development through commercial production and product discontinuation (4,11). The use of a lifecycle approach to pharmaceutical product quality is widely thought to facilitate innovation and continual improvement as well as strengthen the link between pharmaceutical development and manufacturing (ICH Q10). The lifecycle philosophy is fundamental in the ICH guidance documents for Pharmaceutical Develop-