



Technical Report No. 60-3

Process Validation: A Lifecycle Approach

Annex 2: Biopharmaceutical Drug Substances
Manufacturing



Process Validation: A Lifecycle Approach Team

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Table of Contents

1.0 INTRODUCTION	1	5.0 STAGE 3: LIFECYCLE MANAGEMENT	33
1.1 Purpose and Scope	1	5.1 Ongoing Process Verification Approaches	33
2.0 GLOSSARY OF TERMS.....	2	5.2 Transfer of Biopharmaceutical Manufacturing Processes	34
2.1 Abbreviations.....	6	5.2.1 Process Transfer and Adaptation	34
3.0 STAGE 1: BUILDING AND CAPTURING PROCESS KNOWLEDGE — PROCESS DESIGN	6	5.2.2 Product Comparability and Stability	35
3.1 Sequence of Activities Leading Up to Stage 2 – Process Performance Qualification	7	5.2.3 Multisite Manufacturing of Biopharmaceutical Products.....	35
3.2 Analytical Methods	7	6.0 REFERENCES.....	35
3.3 Risk Assessments	9	7.0 APPENDIX 1: EXAMPLE OF FAILURE MODES AND EFFECTS ANALYSIS.....	39
3.4 Platform Technology Application during Development	10	8.0 APPENDIX 2: EXAMPLE OF SCALE-DOWN MODEL QUALIFICATION	40
3.5 Quality Target Product Profile and Critical Quality Attribute Assignment	10	9.0 APPENDIX 3: UNIT OPERATIONS USED IN BIOPHARMA PROCESSES	41
3.6 Control Strategy	12	9.1 Expression Construct and Cell-Line Development and Characterization	41
3.6.1 Risk Assessment to Support Control Strategy Development	13	9.2 Vial Thaw and Cell Expansion (Seed Train)	41
3.6.2 Critical Process Parameters	13	9.3 Production Bioreactor (Fermentation/Cell Culture)	41
3.6.3 Noncritical Process Parameters	13	9.4 Cell Culture.....	42
3.6.4 Process Characterization	14	9.5 Harvest.....	43
3.6.5 Criticality Assessment of Raw Materials.....	16	9.6 Capture Chromatography.....	43
4.0 STAGE 2: PROCESS QUALIFICATION.....	17	9.7 Viral Inactivation.....	43
4.1 Readiness	18	9.8 Polishing Chromatography.....	43
4.1.1 Equipment and Facilities.....	18	9.9 Ultrafiltration and Diafiltration	45
4.1.2 Methods	19	9.10 Drug Substance Filling	45
4.1.3 Raw Materials.....	19	9.11 Single-use Bioreactor Cell Culture	45
4.2 Process Validation	20	9.12 Reactions	45
4.2.1 Process Performance Qualification.....	20	9.13 Conjugation (e.g., Drug, Vaccine).....	45
4.2.2 Process Validation Studies.....	23		
4.2.3 Validation of Single-Use Systems.....	32		

FIGURES AND TABLES INDEX

Table 3.2-1 Examples of In-Process Test and Lot Release Assays	8	Table 9.6-1 Example: Process Parameters and Performance Indicators.....	44
Figure 4.0-1 Activities Leading Up to Process Validation ..	18	Table 9.7-1 Example: Process Parameters and Performance Indicators.....	44
Table 7.0-1 Example FMEA: Failure Modes and Effects Analysis	39	Table 9.8-1 Example: Process Parameters and Performance Indicators.....	44
Table 8.0-1 Scale-Down Variables	40	Table 9.9-1 Example: Process Parameters and Performance Indicators.....	45
Table 8.0-2 Chromatography Column Scale-Down Verification Example	40	Table 9.10-1 Example: Process Parameters and Performance Indicators.....	45
Table 9.2-1 Example: Process Parameters and Performance Indicators.....	42	Table 9.12-1 Example: Process Parameters and Performance Indicators.....	46
Table 9.3-1 Example: Process Parameters and Performance Indicators.....	42	Table 9.13-1 Example: Process Parameters and Performance Indicators.....	46
Table 9.4-1 Example: Process Parameters and Performance Indicators.....	42		
Table 9.5-1 Example: Process Parameters and Performance Indicators.....	43		

1.0 Introduction

Significant advancements in the design and implementation of effective validation programs have taken place since the adoption of the lifecycle concept recommended by the International Council on Harmonisation (ICH), U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMA). The lifecycle approach is detailed in the 2011 revision of the FDA *Guidance to Industry: Process Validation: General Principles and Practices* and the European Commission's update of *Annex 15: Qualification and Validation, Eudralex – Volume 4 (1, 2)*. Then, in 2016, the EMA finalized the *Guideline on Process Validation for the Manufacture of Biotechnology-Derived Active Substances and Data to be provided in the Regulatory Submission* specifically to address biopharmaceutical drug substances (3). These documents refined expectations and aligned process validation practices into the three-stage model now practiced by industry and promoted by regulatory agencies worldwide.

PDA discusses extensively the three-stage approach and its implementation in *Technical Report No. 60: Process Validation: A Lifecycle Approach* and *Technical Report No. 60-2: Process Validation: A Lifecycle Approach, Annex 1: Oral Solid Dosage/Semisolid Dosage Forms (4, 5)*. *PDA Technical Report 60-3: Process Validation: A Lifecycle Approach Annex 2: Biopharmaceutical Drug Substances Manufacturing* continues the series by addressing the implementation of process validation in biopharmaceutical manufacturing. It also serves as an update to and replacement for *Technical Report No. 42: Process Validation of Protein Manufacturing (6)*.

A successful validation program is initiated early in the process development lifecycle and continues until the process and product reaches the end of its lifecycle. The program should be founded on a comprehensive corporate policy that defines an organization's expectations and commitment to process validation principles. This policy should define the corporation's quality management philosophy and identify the components of validation, periodic review or requalification timeframes, documentation requirements (including a validation master plan), validation protocols and reports, and responsibilities of key stakeholders within the organization (7).

Enhanced risk-based approaches, such as quality by design (QbD), recognize the capability of process control strategies to ensure product consistency and prevent or mitigate the risk of producing a poor-quality product (8-10). To illustrate how specific QbD elements can be applied to the validation of biopharmaceutical drug substances, this technical report discusses the use of quality target product profiles (QTPPs), critical quality attributes (CQAs), material attributes, and critical process parameters (CPPs). It also indicates which risk management tools can be used to identify the attributes related to the product and process and describes the relationships that link the product profile to quality, product, material attributes, and process parameters.

1.1 Purpose and Scope

The concepts presented in TR-60-3 are intended to assist in the design and implementation of globally compliant validation programs to ensure process reproducibility and robustness as they relate to biotechnology-derived, purified protein drug substances. These models are based on the material and practices established in TR-60 and global regulatory guidances. Points to consider are provided to facilitate the collection of data in support of a regulatory filing for the approval of a biopharmaceutical drug substance intended to be used in a pharmaceutical product. The science-based practices provided here are grounded in the experiences of a PDA task force comprising a cross-section of industry professionals and experts in the field. The approaches are intended to add value, support good business practices, and meet current compliance and regulatory expectations.

This technical report focuses on the validation of biopharmaceutical processes used to manufacture therapeutic proteins, polypeptides, and vaccine drug substances. These drug substances are produced from recombinant or nonrecombinant cell-culture expression systems and can be characterized using appropriate analytical procedures. This information also applies to biosimilar products and chemically modified