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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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