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BIOPHARMACEUTICAL VALIDATION (BIO08046)

Written Assignment

**Part 1: Elaborate on a typical sequence of process validation activities (from product development to validated process) for a biopharmaceutical product**

The typical process validation activities for a biopharmaceutical product can be classified into three main stages: Process Design, Process Qualification and Continued Process Verification (See Figure1), (USR192162, 2024). Those steps can be viewed as continuous approach in biopharmaceutical validation. This method aligns process validation activities with a product lifecycle concept (FDA, 2011). A framework for all validation activities throughout the entire lifecycle of a product or process is contained in Validation Master Plan (VMP) a high-level document that acts as a guide to ensure reliability and prevent deviations (Todde et al., 2017).

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Figure 1. A visual representation of process validation activities for a biopharmaceutical product (USR192162, 2024).

* 1. **Stage 1: Process Design.**

This stage focuses on defining and understanding the manufacturing process based on development studies. When working through process development and characterisation, it is important to identify the Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs). QTPP serves as the foundation for designing product development. It is a forward-looking outline of the desired quality attributes of a drug product that should be attained to guarantee its intended quality while taking into account its safety and efficacy (Zagalo et al., 2022). Critical Quality Attributes (CQAs) refer to the physical, chemical, biological, or microbiological characteristics that must fall within a specified range, limit, or distribution to maintain the intended quality, safety, and effectiveness of a product (Pallagi et al., 2019). Potential CQAs of a drug substance help steer process development, and this list may be adjusted as process understanding and knowledge evolve (ICH Q11, 2012).

Laboratory and pilot scale studies are crucial for establishing process parameters through small-scale experiments for the validation process. These studies help in understanding the relationship between input variables and Critical Quality Attributes, and in predicting quality at commercial scale (FDA, 2011). Eexperimental data is essential for validation of a model before application in a cell culture process in bioreactors. It ensures it adequately covers the space of operating parameters needed for accurate prediction for successful process scale up (Xing et al., 2024). The development of the manufacturing process should determine which inputs (such as material attributes and process parameters) and outputs (including quality attributes and performance indicators) for each process step or unit operation need further assessment during process evaluation and verification studies (EMA, 2016a).

Critical Process Parameters (CPPs) are process parameters whose variability can impact Critical Quality Attributes and should be monitored or controlled to ensure the desired quality (EMA, 2016a). Process parameters like time, temperatures, agitation rates, working volumes, media feed and induction of production can be a specific CPPs in cell cultures (EMA, 2016b).

The relationship between the process inputs outputs can be described in the Design Space (ICH Q8, 2009). The assurance of quality is achieved through the multidimensional interplay of input variables and process parameters. Operating within the established design space is not regarded as a change; however, any deviation beyond this space is considered a modification and typically requires a regulatory post-approval change process (EMA, 2016b; ICH Q8, 2009; ICH Q11, 2012).

Technology transfer is a critical stage in the product lifecycle, serving as a validation step when moving knowledge and processes from research and development (R&D) to manufacturing. The process entails sharing product and process knowledge from development to manufacturing, as well as between or within manufacturing sites, to ensure successful product realization. This knowledge serves as the basis for the manufacturing process, control strategy, process validation approach, and continuous improvement (ICH Q10, 2008).

Process Control Strategy Development focuses on ensuring process consistency through defined controls. A control strategy is a systematically designed set of controls based on existing knowledge of the product and process to maintain process performance and product quality. These controls include parameters and attributes associated with active substances, materials, components, facility and equipment conditions, in-process controls, final product specifications, and relevant monitoring and control methods (ICH Q8, 2009). The selection and scope of process controls can be informed by prior risk assessments and further refined as more experience with the process is gained (FDA, 2011).

Design Qualification involves defining the commercial manufacturing process based on knowledge gained through development and scale-up activities. It's about designing a process suitable for routine commercial manufacturing that consistently delivers a product meeting its quality attributes (FDA, 2011). Following this step, vendor constructs equipment and systems. The set of specifications defined by the user that acts as a reference for the design and purchase of each piece of equipment, or a facility is described as User Requirement Specification (URS) It outlines significant parameters that the system must meet based on design space. The URS helps define the intended use of the instrument and related acceptance criteria. A URS complies with applicable guidelines and standards and aligns with the Validation Master Plan VMP (Todde et al., 2017).

* 1. **Stage 2: Process Qualification (PQ)**

Process Qualification (PQ) is a crucial phase of process validation that ensures the designed manufacturing process can consistently produce commercial batches. During this stage, manufacturers must comply with Current Good Manufacturing Practice (CGMP) regulations. PQ consists of two key components: facility design and qualification of utilities and equipment, along with Process Performance Qualification (PPQ) (FDA, 2011).

Installation Qualification (IQ) verifies that a facility, system, or instrument has been installed correctly according to the manufacturer’s guidelines and/or user-approved specifications. This process involves reviewing documentation (such as manuals, schematics, and certificates), inspecting electrical and gas connections, and ensuring major components (e.g., valves, tubing, software, pumps, and control panels) are properly installed. IQ confirms that installation aligns with the User Requirements Specification (URS) and manufacturer-provided documentation (Todde et al., 2017).

Operational Qualification (OQ)verifies that a facility, system, or instrument operates properly, and that critical components respond as intended and within the desired range. (Todde et al., 2017). OQ should focus on the most critical components, evaluating how failure or miscalibration could impact the system's performance and the quality/safety of the product (Ghosh et al., 2022).

Performance Qualification (PQ) aims to verify that a facility, system, or instrument performs properly and reproducibly in the intended routine conditions set for the specific preparation process, using approved methods (Todde et al., 2017). PQ is conducted after Installation Qualification and Operational Qualification have been completed (Ghosh et al., 2022). PQ is not only for newly installed instruments but is also performed routinely on working instruments. Testing frequency may be defined at intervals such as weeks, months, or years, depending on user experience and instrument criticality and operating procedures should be in place, including a logbook or electronic record, to document PQ activities (Ghosh et al., 2022).

Process Validation represents the second component of Stage 2, known as process qualification, within the process validation lifecycle. This stage is essential for verifying that the designed manufacturing process can consistently produce commercial batches. It integrates the qualified facility, utilities, equipment, and trained personnel with the commercial manufacturing process, control measures, and necessary components to manufacture Process Performance Qualification (PPQ) batches. The FDA emphasizes that manufacturers should make well-informed decisions regarding the appropriate number of PPQ batches based on their understanding of the product and process (FDA, 2011). One key consideration in determining the required number of PPQ batches is batch-to-batch variability, which can be influenced by multiple factors, including the active pharmaceutical ingredient (API) content or product label claim (Pazhayattil et al., 2016).

**1.3. Stage 3: Continued Process Verification (CPV)**

Continued Process Verification (CPV) is an alternative method of process validation that involves the ongoing monitoring and assessment of manufacturing process performance. This science- and risk-based real-time approach ensures that the process consistently produces material meeting all critical quality attributes (CQAs) and control strategy requirements while operating within predefined parameters. Implementing CPV requires extensive in-line, on-line, or at-line controls, with continuous monitoring of process performance and product quality for each batch. Technologies such as Process Analytical Technology (PAT) and Multivariate Statistical Process Control (MSPC) can facilitate CPV. Additionally, real-time data collected during continuous process verification at the production scale must be available on-site for regulatory inspection (EMA, 2016b).

Annual Product Review (APR) or Continued Process Verification reports are used to assess trends and variability in manufacturing processes. It’s also helps ensure a process remains in a state of control during commercial production (EMA, 2016a). A pharmaceutical company should implement a structured approach to determine the root cause to any deviation. The level of effort, formality, and documentation should align with the level of risk. Corrective Actions and Preventative Actions (CAPA) is a systematic process used to identify and address issues, prevent their recurrence, and drive continuous improvement,resulting from the investigation of complaints, product rejections, and other factors (ICH Q10, 2008).

* 1. **Cleaning and Sterilisation Validation**

Validating cleaning and sterilization procedures is essential in biopharmaceutical production to maintain product quality and safety. Process validation, in general, involves collecting and assessing data from the process design stage through commercial manufacturing to provide scientific evidence that a process can consistently produce a high-quality product (FDA, 2011). The primary goal of cleaning validation is to establish documented proof that an approved cleaning procedure effectively prepares equipment for pharmaceutical manufacturing. Its objective is to ensure a reliable cleaning process, reducing the need for routine analytical monitoring. Cleaning validation aims to demonstrate that residues whether chemical, radiochemical, or microbiological are effectively removed to a specified level from equipment, ensuring compliance with product quality standards and preventing contamination from reagents or solvents used during preparation (Todde et al., 2017).

Cleaning procedures for equipment’s product contact surfaces typically require validation. Attention should also be given to non-contact parts that could potentially meet the product. Cleaning procedures for product changeover must be thoroughly validated. The varying properties and impurity profiles of raw materials from different suppliers should be considered when developing cleaning procedures (European Commission, 2015). Risk-based approach can be used to manage risks associated with starting materials and cleaning agents, and to determine how residues are effectively removed and detected (EMA, 2016a). A Cleaning Validation Protocol is required, outlining how the cleaning process will be validated. This protocol should include aspects such as: the objective and responsibilities; description of the equipment and cleaning procedures; the interval between the end of production and the start of cleaning; the number of consecutive cleaning cycles to be performed (at least three are generally recommended); routine monitoring requirement; sampling procedures, including rationale and locations; analytical methods, including limits of detection and quantification; acceptance criteria and their rational; considerations for bracketing different products, processes, and equipment; when re-validation will be required (European Commission, 2015).

Sterilization equipment, such as autoclaves and hot air ovens, must be appropriate for their intended purpose. Temperature probes used to monitor sterilization cycles should be properly calibrated. Qualified biological indicators must be used for verification (FDA, 2011). Records of maintenance and cycle runs should be maintained. The sterilization method for sterile components and disposable items (e.g., filters, bags, containers, stoppers) must be suitable, and proper documentation supporting their use and shelf life should be established. Final sterile drug products should not be released until sterility testing results are satisfactory. However, for products with short shelf lives (e.g., radiopharmaceuticals, cellular products), release may occur based on other relevant tests while awaiting sterility test results, with an investigation conducted if sterility test results are positive (FDA, 2008).

In the context of biopharmaceutical manufacturing, both cleaning and sterilisation validation are integral parts of overall process validation, which follows a lifecycle approach from process design through commercial production. These validation activities are crucial for ensuring that the manufacturing process consistently produces a product that meets its predefined specifications and quality characteristics. Regulatory guidelines from authorities like the EMA and FDA provide frameworks and expectations for these validation processes (EMA, 2016a; FDA, 2011).

* 1. **Risk Management**

In a typical process validation sequence, risk management plays a critical role at various stages. The Quality Risk Management (QRM) process involves risk assessment, control, communication, and review throughout the product lifecycle (ICH Q9, 2023). During the Process Design stage, QRM can be applied in several activities, including evaluating options for the manufacturing process design, assessing quality attributes and process parameters, and enhancing the confidence in consistently producing batches of the desired quality (ICH Q11, 2012). In the Process Qualification stage, risk management helps prioritize specific qualification activities and determines the level of effort required for both performance and documentation (FDA, 2011). A risk-based approach can demonstrate how the variability of raw materials and their associated risks are managed throughout the product lifecycle, with ongoing reassessments as process understanding improves (EMA, 2016a).

Risk assessment tools include facilitation methods like flowcharts, check sheets, Failure Mode Effects Analysis (FMEA), Fault Tree Analysis (FTA) and others. FMEA is a method that prioritizes variables based on their probability, severity, and detectability, offering an evaluation of possible failure modes, the factors contributing to these failures, and their potential impacts on outcomes and product performance (Zagalo et al., 2022). FTA assumes failure of a product or process function and evaluates system failures by identifying causal chains. It represents results pictorially as a tree of fault modes. Risk ranking and filtering can be also utilized to prioritize manufacturing sites for inspection or audit (ICH Q9, 2023).

* 1. **Quality by Design (QbD)**

Process validation and the Quality by Design approach are interconnected methodologies aimed at ensuring pharmaceutical product quality (FDA, 2011). Process validation is the process of gathering and analysing data from the design phase through commercial production to provide scientific evidence that a process can consistently produce a high-quality product (FDA, 2011). The Quality by Design (QbD) approach is a structured development methodology that starts with predefined goals and focuses on understanding the product and process, as well as controlling the process based on solid scientific principles and quality risk management (ICH Q8, 2009). The QbD approach provides a structured framework for process design and development, which in turn enhances the effectiveness of process validation (See Figure 2). By integrating QbD principles, pharmaceutical manufacturers can achieve better process understanding, improved product quality, and greater regulatory success (Zagalo et al., 2022).

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Figure 2. A visual representation of the Quality by Design approach in process validation (Zagalo et al., 2022).

* 1. **Conclusion**

Based on the preceding sections, it can be concluded that biopharmaceutical process validation is a critical and multifaceted activity that spans the entire product lifecycle, from initial process design through to ongoing commercial production. This lifecycle approach, encompassing Process Design, Process Qualification, and Continued Process Verification, ensures a continuous focus on understanding and controlling the manufacturing process to consistently deliver high-quality biopharmaceutical products.

Key to this process are the early definition of the Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs), which guide process development and characterisation. Understanding the relationship between input variables and CQAs through laboratory and pilot scale studies is crucial for establishing Critical Process Parameters (CPPs) and the Design Space, within which process operation assures quality.

Process Qualification is a crucial phase that ensures the manufacturing process can consistently produce commercial batches, including the design of the facility and the qualification of utilities and equipment, leading to the production of Process Performance Qualification (PPQ) batches. The Continued Process Verification (CPV) approach focuses on the continuous monitoring and assessment of process performance.

Furthermore, the validation of cleaning and sterilisation procedures is indispensable for ensuring product safety and quality by demonstrating the effective removal of residues and the sterility of equipment and components.

The integration of Quality Risk Management throughout all stages is essential for identifying, assessing, and controlling potential risks to product quality. Tools such as FMEA and FTA aid in this risk-based approach.

Finally, the Quality by Design approach provides a structured framework for process development and enhances the effectiveness of process validation by emphasising product and process understanding and control.

In essence, the effective biopharmaceutical process validation relies on a holistic, science-based, and risk-managed approach that ensures consistent product quality throughout the product lifecycle, guided by regulatory expectations and best practices. The Validation Master Plan (VMP) serves as the overarching document to ensure all validation activities are conducted reliably and deviations are prevented.

**Part 2: Compare and contrast the** **process validation requirements** **for a traditional, stainless-steel bioprocess versus a single-use/disposable technologies bioprocess**

General process validation approach ensures a bioreactor system consistently performs as intended, producing a product that meets predetermined specifications and quality attributes. This involves: Design, Qualification and Continued Process Verification (ICH Q11, 2012; EMA, 2016a).

**2.1.** **Stainless-Steel Bioprocess (SSB)**

Stainless-Steel Bioprocess validation requirementsinvolve rigorous design, selecting materials that withstand high temperatures and harsh cleaning agents.Ensures proper mixing, aeration, and control of temperature, pH, and dissolved oxygen (Dua et al., 2021).

In terms of Qualification equipment Requires extensive Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) for large-scale fixed systems. A key component of stainless-steel bioreactor validation is cleaning and sterilization validation. It is mandatory and ensures cleaning procedures effectively remove residual contaminants (Todde et al., 2017).

Stainless-steel systems require extensive continuous monitoring to ensure process consistency and detect deviations (EMA, 2016a).Computational Fluid Dynamics (CFD) models and experimental validation (e.g., volumetric oxygen transfer coefficient, kLa) are used to maintain control (Xing et al., 2024).

In terms of economic and operational considerations it includes high initial capital investment but long-term cost savings due to reusability. Significant facility requirements, including water and energy consumption (www.bioprocessintl.com, n.d.).

**2.2. Single-Use Bioprocess (SUB)**

Single-Use Bioprocess validation requirements must address variability in polymeric materials and raw materials impact on product quality (EMA, 2016a). Single-use bioreactors require assessment of Extractables and Leachables (E&L) to avoid adverse effects on bioprocessing (Diao et al., 2024).

Qualification process is simplified and pre-validated by vendors; simplified IQ/OQ/PQ due to modular and disposable nature (Todde et al., 2017). Demonstrating comparability for Single-Use technologies with traditional bioreactors is crucial for regulatory acceptance (Beck et al., 2020). The equivalence testing is required to demonstrate that product quality and cell culture performance are comparable between SSBs and SUBs (Beck et al., 2020). Evaluation of hydrodynamics using Euler-Lagrange modelling and CFD simulations to ensure equivalent performance to stainless steel systems (Delafosse et al., 2018). Two One-Sided Test (TOST) statistical analysis is also commonly used to establish comparability (Beck et al., 2020).

Unlike stainless steel, cleaning validation is largely eliminated. Risk assessment shifts to ensuring disposable components do not introduce contaminants or variability into the process (Todde et al., 2017).

Similar to SSB, Continuous Process Verification real-time monitoring using Process Analytical Technology (PAT) and Multivariate Statistical Process Control (MSPC) is essential (EMA, 2016a).

Single-Use technologies are associated withlower capital expenditure, smaller facility footprint, and faster implementation compared to SSBs. It also eliminates cross-contamination risks and reduces downtime between batches. However, disposal and environmental impact considerations must be managed (www.bioprocessintl.com, n.d.).

Table1. Represents key differences for process validation requirement for a stainless-steel bioprocess versus a single-use technologies bioprocess (Diao et al., 2024; Todde et al., 2017; www.bioprocessintl.com; Xing et al., 2024).

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| **Aspect** | **Stainless-Steel Bioprocess (SSB)** | **Single-Use Bioprocess (SUB)** |
| Capital Cost | High initial investment, long-term savings | Lower capital expenditure, higher recurring costs |
| Cleaning & Sterilization | Extensive cleaning validation required | No cleaning validation, but E&L assessments needed |
| Cross-Contamination Risk | Potential risk; mitigated by strict procedures | Eliminated due to disposable components |
| Implementation Time | Lengthy due to facility build-out | Faster due to pre-sterilized disposable systems |
| Environmental Impact | High water/energy consumption | Waste generation due to disposables |
| Process Monitoring & Control | Requires continuous monitoring and validation | Real-time monitoring with PAT and MSPC |
| Regulatory Considerations | Well-established validation pathways | Emerging requirements, comparability studies essential |

**2.3. Conclusion**

Process validation is crucial for both SSB and SUB, focusing on Design, Qualification, and Continued Process Verification. However, their specific requirements differ significantly.

SSB validation necessitates rigorous design for durability, extensive IQ/OQ/PQ, and mandatory, complex cleaning and sterilisation validation. Continuous monitoring is vital for control. SSBs involve high initial costs but potential long-term savings, with substantial facility and resource needs. Cross-contamination is a potential risk managed by procedures.

Conversely, SUB validation addresses polymeric material variability and E&L concerns. Qualification is simpler due to pre-validated components. Cleaning validation is largely eliminated, with risk shifting to disposable component integrity. Comparability with SSB is essential for regulatory acceptance, often using equivalence testing and statistical analysis. SUBs offer lower initial capital expenditure and faster implementation, eliminating cross-contamination risks. However, they generate waste and have emerging regulatory requirements.

In essence, SSB prioritises robust, reusable systems with intensive cleaning validation, while SUB emphasises flexibility, speed, and eliminating cleaning, but requires careful material management and comparability assessments. Both demand thorough validation to ensure consistent biopharmaceutical production.

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