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Ensuring Quality in Biopharmaceutical Development: A Phase-Appropriate GMP Approach

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Abstract

This review offers a comprehensive examination of Good Manufacturing Practices (GMPs) across the entire product life cycle. GMPs evolve in stringency from discovery and research and development (R&D) stages through clinical trials to commercial launch, known as the "Phase-Appropriate" Approach. This framework aids sponsors in producing safe clinical materials while retaining manufacturing flexibility, particularly for noncommercial scales. The article emphasizes the necessity of a dedicated quality system during the R&D phase to ensure compliance and manage documentation. Focusing on phase-appropriate current Good Manufacturing Practices (cGMP) for therapeutic protein drug substances, the review highlights strategies for maintaining cGMP compliance during clinical studies and ensuring Chemistry, Manufacturing, and Controls (CMC) submission requirements are met. Ultimately, it aims to guide the development of a pharmaceutical quality system that assures the safety and quality of products intended for clinical trials.

Keywords:

Good Manufacturing Practices (GMP);
Phase-Appropriate Approach;
Quality Systems;
Clinical Trails Manufacturing;
Risk-Based Approach.

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1. Introduction

This review aims to provide an extensive overview of Good Manufacturing Practices (GMPs) across the entire product life cycle. GMPs are essential guidelines that become progressively stricter as a product advance from the discovery and research and development (R&D) stages, through clinical trials, and finally to commercial launch. This progressive stringency is often referred to as the "Grade" or "Phase-Appropriate" Approach.

The report also outlines a basic framework for clinical trial manufacturing, particularly for facilities where full commercial development or manufacturing may not be the primary objective, such as universities, grant-funded investigators, and startup biotech firms. The phase-appropriate approach is designed to help sponsors provide safe clinical materials for human studies while maintaining manufacturing flexibility at noncommercial scales and during the transition to commercial-scale facilities. Some companies find it beneficial to establish a dedicated development or R&D quality system that oversees the quality and compliance of clinical materials and manages the documentation process.

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1.1 Purpose and Scope

The primary objective of this article is to define current Good Manufacturing Practice (cGMP) principles for the production of pre-market therapeutic bulk substances. It also aims to provide examples of approaches for maintaining cGMP compliance during clinical studies.

This review focuses on phase-appropriate cGMP during the production of therapeutic protein drug substances, from the R&D stage through the completion of phase 3 clinical trials. Additionally, it includes the implementation of a pharmaceutical quality system that ensures the safety and quality of products intended for clinical trials. The goal of implementing a phase-appropriate cGMP-compliant quality system is to ensure that Chemistry, Manufacturing, and Controls (CMC) submission and dossier requirements for therapeutic proteins at the pre-marketing phase are adequately addressed. However, cGMP requirements for finished drug product manufacturing are beyond the scope of this review.

2. Glossary of Terms

Active Pharamaceutical Ingredient (API)
Any substance or mixture of substances intended to be used in the manufacture of a drug/medicinal product and that, when used in the production of a drug, becomes an active ingredient of the drug product.Such substances are intended to furnish pharmacologicalactivity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

Biological Active Substance
Manufactured biological active substances and medicinal products involving biological processes and materials, such as cultivation of cells or extraction from living organisms.

Biologics License Application (BLA)
An application, filed with the U.S. Food and Drug Administration (FDA), which contains specific information on the manufacturing process, chemistry, pharmacology, clinical pharmacology and the medical effects of the biological product.

Certificate of Analysis (CoA)
the certificate by a supplier of the performance of the material tested against a set of specifications such as identity priority, moisture content, pH, color, by burden, endotoxin, etc.

Chemistry Manufacturing and Controls (CMC)
the body of information that defines the technical development, manufacturing facility and support utilities; the process equipment and materials used in manufacturing; the manufacturing process itself; the personal involved in manufacturing and quality; the chemistry of the product; QC in process and release testing, specifications and stability of the product; all of the controls, documentation and training necessary to ensure that all of this listed activities are properly and effectively carried out.

Critical quality attribute (CQA)
physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality, as defined in ICH quality guidance Q8.

Critical Process Parameter (CPP)
An input process parameter that should be controlled within a meaningful operating range to ensure that drug substance critical quality attributes meet their specifications. Although parameters with wide operating ranges may also impact product quality they are generally easily controlled and not as likely to result in excursions.

Current Good Manufacturing Practices (cGMP)
Current GMP Provides for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations*(1).*

Early Phase
Generally used to indicate phase 1 and A clinical studies.

Good Documentation Practice
commonly abbreviated GDP. Describes standards by which documents are created and maintained.

Method Qualification
Formal or informal study performed to assess initial method performance prior to full validation; assessment activity that culminates inascientifically sound method that has an acceptable level of performance and is documented to be suitable for its intended use*(11).*

Method Validation
A formal, archived demonstration of the analytical captivity of an assay that provides justification for use of the essay for an intended purpose.

New Drug Application (NDA)
An application filed with the FDA used for the regulation and control of new drugs in the United states; the goal is to provide enough information to permit the FDA reviewer to reach the following key decisions: whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks; whether the drugs proposed labeling is appropriate, and what it should contain; whether the methods used in manufacturing a drug, and the controls used to maintain the drugs quality are adequate to preserve their drugs identity, strength, quality and purity*(14).*

Phase 1 Clinical Trials
Phase 1 Trials are the first stage of testing in human subjects. Often, a small (20-100) group of healthy volunteers will be selected. For life threatening indications such as oncology, these can be patients that have the target disease but may not yet be the ideal target population. This phase includes trials designed to assess the safety tolerability, pharmacokinetics and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff.

Phase 2 Clinical Trials
Once the initial safety of this study drug has been confirmed in Phase 1 trials, Phase 2 trials are performed on larger groups (20-300) and are designed to assess efficacy, as well as to continue safety assessments in a larger group of volunteers and patients. Phase 2a is specifically designed to assess dosing requirements. Phase 2b trials are specifically designed to study efficacy.

Phase 3 Clinical Trials
final clinical stage Phase 3 trials are designed to demonstrate the potential advantages of the new therapy; safety and efficacy of the new therapy have studied overall longer period of time and more patients (1,000-3,000) Are enrolled in the study with less restrictive eligibility criteria. Phase 3 studies are intended to help scientists identify rarer side effects of treatment and prepare for a broader application of the product.

Pharmacokinetics
How the body processes the drug the study of the movement of drugs in the body, including the process of absorption, distribution, localization in tissues, biotransformation and excretion.

Pharmacodynamics
how the drug works in the body, the biochemical and physiological effects of drug and its mechanisms of their actions.

Process Validation
the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product*(15).*

Product Characterization
The characterization of quality attributes, such as peptide map, glycosylation, chromoatography profile, moelcula weight, gel chromatogram, polymorphs, etc.

Qualified Person (QP)
An individual, as defined in the European Union pharmaceutical regulation as described in Directive 2001/83/EC that has the legal responsibility for batch release of medicinal products.
Note:Refer to EU GMP Annex 16, Certification by a qualified person and batch release.

Specification
A list of tests references to analytical procedures, an appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Toxicity studies
In vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions with the primary goals of identifying:1) an initial safe dose of subsequent dose escalation schemes in humans;2) potential target organs for toxicity and for the study of whether such toxicity is reversible; and 3) safety parameters for clinical monitoring after the appropriate dosing and administering schedule is followed.

3. Role of Quality System

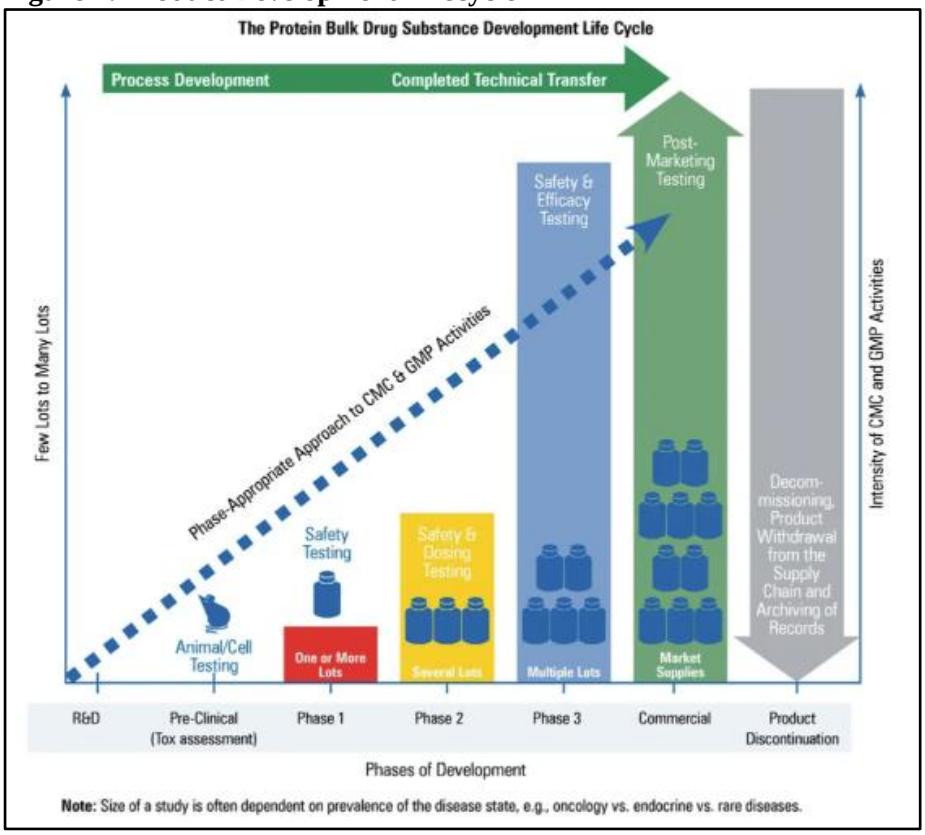
The quality of protein drug products used in clinical trials heavily depends on the quality of the protein drug substances they are made from. A robust quality system provides the necessary framework to ensure that all relevant current Good Manufacturing Practices (cGMP) and regulatory Chemistry, Manufacturing, and Controls (CMC) requirements are met. Such a quality system, when combined with comprehensive product development knowledge, guarantees product quality and patient safety. An effective quality system ensures adherence to all cGMP and regulatory CMC requirements.

3.1 Development Life Cycle

During the non-clinical and clinical phases of product development, new drug supplies are manufactured for investigative programs. These materials, intended for human use, must possess the necessary quality attributes for proper clinical evaluation. As investigational activities progress, process development should also occur in parallel, aiming to create a commercially viable, cGMP-compliant process.

The main goal of process development is to design, develop, and characterize processes and products that can transition to a commercial environment, supporting consistent, high-quality production. The drug substance is a critical component influencing the final quality of the drug product. A new product's life cycle spans from discovery through discontinuation, with the intensity of cGMP activities increasing as process knowledge and understanding are gained during development. Some cGMP aspects, such as instrument calibration and documentation practices, start early, while others, like commercial process validation, occur later in development.

Figure 1: Product Development Lifecycle



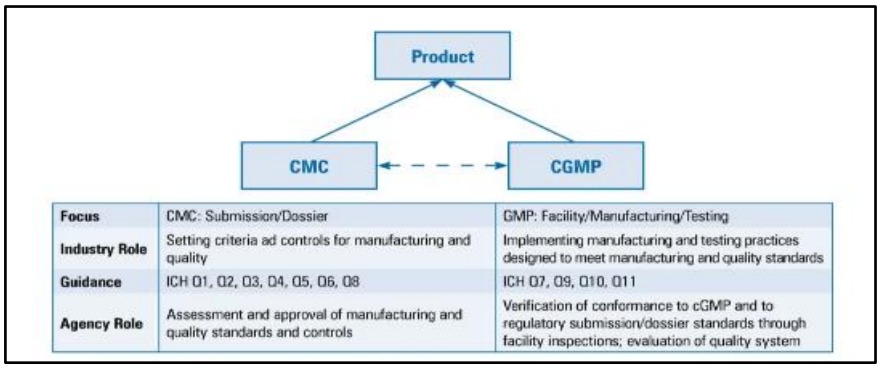
3.2 Relationship between Process Criticality and Risk

Risk assessment includes evaluating the severity of potential harm, the probability of occurrence, and detectability. The level of risk can change through mitigation measures. During technical development, defining Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) is crucial. Any failure or risk associated with a CPP can directly impact one or more CQAs, so these risks must be well understood, controlled, and monitored. While the failure of non-critical parameters may not affect CQAs, it could impact attributes such as manufacturing yields. Therefore, understanding and managing the impact of non-critical parameter failures is also important*(8)*.

3.3 Activities during Late Phase 3 Clinical Studies

During the late Phase 3 clinical studies, process development and validation are crucial. These activities aim to design a manufacturing process and demonstrate its reliability in consistently producing a quality product. According to the FDA's 2011 Guidance on Process Validation, this includes collecting and evaluating data from the design stage through production. This data establishes scientific evidence that the process can consistently deliver a quality product. Typically, process validation at a commercial scale begins towards the end of Phase 3 clinical trials with the production of Process Performance Qualification (PPQ) batches.

Figure 2: Relation between cGMP and CMC to ensure Product Quality



Focus	CMC: Submission/Dossier	GMP: Facility/Manufacturing/Testing
Industry Role	Setting criteria ad controls for manufacturing and quality	Implementing manufacturing and testing practices designed to meet manufacturing and quality standards
Guidance	ICH Q1, Q2, Q3, Q4, Q5, Q6, Q8	ICH Q7, Q9, Q10, Q11
Agency Role	Assessment and approval of manufacturing and quality standards and controls	Verification of conformance to cGMP and to regulatory submission/dossier standards through facility inspections; evaluation of quality system

3.4 Continual Process Improvement

Continuous process improvement is essential from the start of product development through to commercial manufacturing. During the pre-marketing phase, product quality should be continuously enhanced. The quality requirements become stricter as the product moves towards late-stage clinical trials and licensure. Ensuring quality at each stage provides a solid foundation for subsequent stages. Flexibility in managing and documenting process improvements is critical for successful development and scale-up.

4. Application of Phase-Appropriate Approach

QualityImplementing a quality system and cGMP using a graded approach is essential from the beginning to the end of clinical trials. This involves five stages:

1. Discovery Research: Creating and evaluating the protein molecule in a lab.
2. Toxicity Studies: Gaining initial in vivo safety data in animal models.
3. Phase 1 Trials: Focusing on evaluating product safety in humans.
4. Phase 2 Trials: Determining dosage, pharmacokinetics, and initial efficacy in humans.
5. Phase 3 Trials: Testing multiple batches in larger human trials to evaluate safety and efficacy, supporting commercialization.

During clinical testing, the emphasis is on product safety and activity. Implementing cGMP principles should start early, ensuring documented calibration, maintenance, and cleaning of equipment. As more product batches are produced and understanding improves, cGMP implementation should become more stringent, preparing for commercial production.

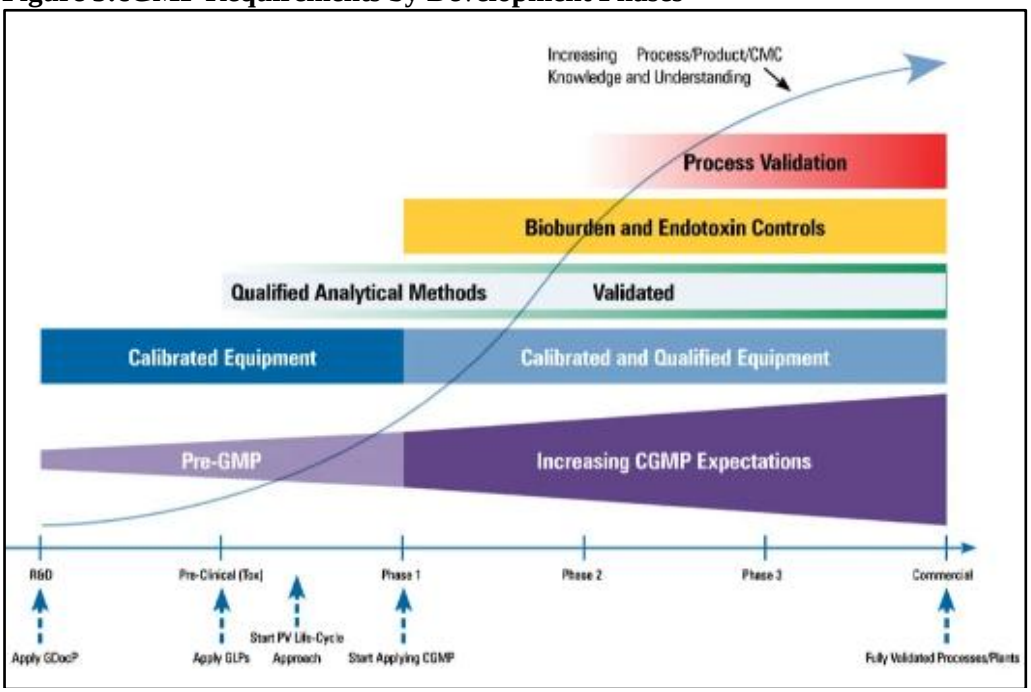
In Phase 1, basic cGMP principles like documentation and equipment operation are followed, though less detailed than in Phase 3 or for Biologics License Applications (BLA). Analyzing demonstration lots at bench and pilot scales with qualified methods and SOPs helps set initial specifications for GMP lot release. Using compendial-grade raw materials from reliable suppliers is essential, with documentation on the origin of materials starting from the R&D stage. Before producing conformance batches, facility and equipment systems, material handling, cleaning, and analytical methods must be fully qualified and validated.

4.1 Level of GMP across Different Organizations

Biopharmaceutical development involves three main types of organizations conducting clinical trials:

1. Large Pharma/Biopharma Firms: These organizations aim to take a product from discovery through marketing.
2. Startup Firms: These entities focus on progressing products from discovery through Phase 1-2 before selling to another firm or expanding to Phase 3.
3. Universities/Grant-Funded Investigators**:** These groups conduct small clinical trials for publication purposes.

Figure 3:cGMP Requirements by Development Phases



Startup firms operate between large biopharma companies and academic institutions. In small lab environments, the GMP system should emphasize basic quality principles, such as documenting production and testing results, facility and equipment qualification, analytical method reliability, and selecting appropriate materials. Poor compliance in early production stages can lead to variability in study materials, affecting patient safety and data integrity. A risk-based assessment of the quality system for clinical material production is recommended to identify and mitigate risks, ensuring data integrity practices are upheld during early production stages.

4.2 General Requirements for Documentation

Effective documentation is a crucial aspect of drug development. It encompasses the recording of process development activities conducted before clinical supply manufacturing, the improvements made during clinical trial material production, and the eventual technology transfer to commercial manufacturing. Proper documentation practices include using indelible ink, making corrections without obscuring the original entries, and signing and dating all documents legibly. These practices ensure traceability and accountability.

Standardized procedures and checklists should be utilized wherever possible, becoming increasingly important in later stages of product development. This standardized documentation aids in maintaining consistent quality and regulatory compliance. Additionally, product development information, which includes the history and understanding of the product, is essential and should be well-documented at the time of performance. Laboratory notebooks or protocols should be maintained diligently, with some countries requiring a second person to countersign these documents to protect intellectual property. All data, especially those used in key technical reports and registration documentation, must be verified by a qualified individual to ensure accuracy and integrity. These records should be securely stored and readily accessible for review. Creating hard or electronic copies of critical original development records is also advisable.

4.3 Product Control

The product control strategy focuses on maintaining the quality of drug substances and materials used in production. It should outline how in-process controls and the management of raw materials, starting materials, intermediates, components, and container closure systems contribute to the final product's quality. This strategy should evolve with product and process knowledge, ensuring the product remains suitable for human clinical trials and eventual commercial production.

A comprehensive product control strategy includes end-product and in-process testing to confirm acceptable product quality and consistency at release and throughout its shelf life. As product development progresses, analytical methods may evolve, and any changes must be assessed to ensure they remain consistent with established criteria. This approach ensures that the product quality is maintained from development through commercialization.

4.4 Toxicity Study Phase

To minimize variability in toxicity study batches due to poorly characterized cells, it is recommended to use qualified cell banks or a working cell bank when available. Research cell banks can be used if their purity is confirmed and their history well-documented. Whichever cells are used, their method of testing and history must be documented to support their use in manufacturing.

During toxicity studies, the manufacturing process and analytical methods may not be fully developed or optimized. However, since the results of these studies form the safety basis for the first human dose, the analytical test methods must be scientifically sound and suitable for their intended use. Materials used in GLP toxicity studies must comply with cGMP requirements and be tested using qualified assays.

The manufacturing process should be described in a pre-approved batch record or protocol, detailing the manufacturer and control of the batch to a level that allows future replication. Any unexpected events or deviations from the protocol should be documented. Companies or academic institutions may opt to outsource the preparation of these materials to ensure controlled production conditions if internal capabilities are lacking.

In some cases, materials manufactured for toxicity studies may be requested for clinical studies. A thorough analysis of the procedures, in-process controls, and documentation is necessary to ensure they meet the required standards. Some companies prefer to manufacture materials for toxicity studies in a GMP facility to reduce production failures and benefit from additional analytical data, ensuring consistent materials.

4.5 Clinical Supply Material

From Phase 1 onwards, cGMP controls must be applied to ensure the drug substance meets purity and potency criteria, reducing patient safety risks. All clinical supplies must be manufactured under conditions fulfilling essential cGMP requirements appropriate for the manufacturing phase and scale. This includes performing extractable/leachable material testing for storage and plastics used during manufacturing as the drug substance progresses from development to clinical use.

Manufacturing process understanding should increase from R&D through Phase 3. Information on proven acceptable ranges, critical quality attributes (CQAs), and critical process parameters (CPPs) should be documented and assessed for commercial implementation. Identifying appropriate CQAs and CPPs depends on the molecule's properties and the impact of specific process parameters on CQAs.

A risk-based approach should be used when performing process validation studies, ensuring statistical confidence in process validation. Data from early development phases may be needed to provide a statistically valid number of data points. The concept of increasing cGMP requirements over the drug substance development lifecycle ensures readiness for commercial production, as illustrated in ***Figure 1***.

5. Conclusion

The review underscores the pivotal role of Good Manufacturing Practices (GMPs) throughout the biopharmaceutical product lifecycle, emphasizing a phase-appropriate approach that intensifies regulatory adherence as products advance from R&D through clinical trials to commercialization. This method ensures that the quality of therapeutic protein drug substances is maintained at every stage, aligning with regulatory expectations and guaranteeing patient safety. Establishing a robust quality system early in the R&D phase is critical, as it provides the necessary framework for compliance, efficient documentation management, and a seamless transition to commercial-scale production.

A significant focus of the review is the implementation of a risk-based approach through Quality by Design (QbD), which enhances the control of critical process parameters (CPPs) and critical quality attributes (CQAs). By understanding and managing these elements, organizations can mitigate risks and ensure consistent product quality. The article also highlights the importance of a comprehensive product control strategy that evolves with increased product and process knowledge, ensuring the quality and safety of drug substances used in clinical trials. This strategic approach is crucial for maintaining the integrity of clinical materials and supporting the successful commercialization of new therapies.

In conclusion, the adoption of phase-appropriate cGMPs and a dedicated quality system is essential for biopharmaceutical companies aiming to produce high-quality therapeutic protein drug substances. By adhering to stringent regulatory guidelines and employing a risk-based approach, organizations can ensure the safety and efficacy of their products throughout the product lifecycle. The review provides invaluable insights and practical guidance for developing and validating biopharmaceutical processes, ultimately supporting regulatory compliance and operational excellence. As the industry continues to evolve, these principles will remain fundamentalin achieving successful outcomes in clinical trials and beyond.

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