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Orignal Article

REGULATORY CONSIDERATIONS FOR BIOTHERAPEUTICS: FOCUS ON CHEMISTRY, MANUFACTURING AND CONTROLS: A REVIEW

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Abstract: ***Biotherapeutics, also known as biologics, are therapeutic agents derived from living organisms. They include a wide range of products such as monoclonal antibodies, recombinant proteins, gene and cell therapies. Due to their complex nature and unique manufacturing processes, biotherapeutics have specific regulatory requirements to ensure their safety, efficacy, and product quality. The production of biotherapeutics is a complex and highly regulated process that requires a deep understanding of molecular biology, cell culture, and protein chemistry. As the demand for these life-saving therapies continues to grow, ongoing research and innovation in the field of biotherapeutics production will be essential to ensure the development of safe, effective, and affordable treatments for a wide range of indications, including cancer, autoimmune disorders, and infectious diseases. The health authorities in the major regions have guidelines and regulations in place to ensure that the manufacture of biologic drugs is in compliance with Good Manufacturing Practices (GMP), and appropriate measures are in place for the chemistry, manufacturing and controls (CMC) of these therapeutics. Regulatory CMC considerations play a crucial role in the development, manufacturing, and approval of biotherapeutics. By understanding and addressing these considerations, companies can ensure the quality of their biotherapeutic products, ultimately benefiting patients and healthcare providers worldwide. As the field of biotherapeutics continues to advance, it is essential for regulatory agencies and developers to collaborate and adapt to the unique challenges and opportunities presented by these groundbreaking therapies.***

Keywords: Biotherapeutics

Dr. Alpana Gupta has about 25 years of experience in the pharmaceutical industry, developing drugs in major therapeutic areas. After completing Ph.D. she moved to the US, as a Research Associate at New York Medical College, NY and Bayer Diagnostics division, NY. At present she is working in Regulatory Affairs at Boehringer Ingelheim Pharmaceuticals, which is a big pharma company headquartered in Germany

Dedication: *The credit for who I am today, and what I have achieved professionally, goes to my beloved Dad. I am deeply indebted, and will forever be grateful for what he has done for me. This article is dedicated to him on his 85th Birthday.*

Manufacture of biotherapeutics: The production of biotherapeutics involves a series of intricate steps, from the initial design of the molecule to the final purification (drug substance - DS) and formulation (drug product - DP). Manufacturing of biologics is more challenging than for traditional small molecule drugs because biologics are generally made in genetically engineered cells that impose their own variability (such as post-translation modifications) on the processes used to make such drugs [1]. Characteristics and properties of drugs produced in living organisms are heavily influenced by the manufacturing process because living cells and organisms are acutely sensitive to changes in their environment and handling procedures. Even minor variations in the manufacturing process can cause significant changes in the safety profile of biologics, and the way it functions in the body, leading to changes in efficacy as well. Effectiveness of the product in patients can also be impacted by the process by which they are manufactured because of the heterogeneity of the molecules, e.g., inherent variabilities of biologic drugs include glycosylation, phosphorylation, deamination, methylation, acetylation, oxidation, etc [2]. A single monoclonal antibody can have millions of molecular variants based on post-translational modifications, and any one of these could potentially affect the binding of the molecule to its target, leading to variations in efficacy. Therefore, manufacturers of biologics need to test for drug safety and efficiency after every change made to their manufacturing process. Not only that, biologics manufacturers must tightly control the source and nature of starting materials, and consistently employ a myriad of process controls that assure predictable manufacturing outcomes.Process controls for biologics are established separately for each unique manufacturing process/product, and are not applicable to a manufacturing process/product created by another manufacturer. Therefore, it is said for biologics that "the process is the product." The production of biotherapeutics can be broadly divided into the following stages:

1. **Design and development:** The first step in the production process is the design and development of the biotherapeutic molecule. This involves identifying a target protein or molecule that can be used to treat a specific disease or condition. Researchers then use various techniques, such as recombinant DNA technology, to create a gene encoding the desired therapeutic protein [3].

2. **Expression systems:** Once the gene encoding the therapeutic protein has been designed, it must be introduced into a suitable expression system. Expression systems are living organisms, such as bacteria, yeast, or mammalian cells, that can produce the desired protein. The choice of expression system depends on the complexity of the protein (e.g. post-translational modifications required) and the desired yield.

3. **Cell culture and fermentation:** After the gene has been introduced into the expression system, the cells are cultured and allowed to grow and multiply. During this process, the cells produce the therapeutic protein, which can then be harvested and purified. The cell culture and fermentation process must be carefully controlled to ensure optimal growth conditions and protein production.

4 **Purification:** Once the therapeutic protein has been produced, it must be purified to remove any contaminants (both, process as well as product related), such as host cell proteins, DNA, endotoxins, Protein A, etc. This is a critical step in the production process, as the purity of the final product directly impacts its safety and efficacy. Various chromatography techniques, such as ion exchange, size exclusion, and affinity chromatography, are used to separate the desired protein from contaminants. This purified protein is commonly referred to as the bulk DS.

5 **Formulation and stability:** After purification, the therapeutic protein is formulated into a stable and effective drug product. This may involve the addition of stabilizers, buffers, antioxidants, or other excipients to ensure the protein remains stable and active during storage and administration. The formulation process must be carefully optimized to maintain the integrity of the protein and ensure its therapeutic efficacy.

Quality control and regulatory compliance: The manufacture of biotherapeutics is subject to strict quality control measures and regulatory oversight to ensure the safety and efficacy of the final product. This includes regular monitoring of the production process, rigorous testing of the final product, and adherence to Good Manufacturing Practices (GMP). Regulatory agencies such as the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Japan's Pharmaceuticals and Medical

Devices Agency (PMDA) have established guidlines and requirements for the development, manufacturing, and approval of biotherapeutics. These guidelines are designed to ensure that biotherapeutics meet the highest standards of safety, efficacy, and quality [4,5].

Key regulatory agencies: The regulatory landscape of biotherapeutics is overseen by various agencies worldwide, with the primary goal of ensuring the safety, efficacy, and highest possible quality of these products [6,7]. Some of the key regulatory agencies include:

1. The United States Food and Drug Administration (FDA), 2: The European Medicines Agency (EMA), 3: Health Canada (HC), 4: The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, 5: The China National Medical Products Administration (NMPA).

These agencies have established guidelines and requirements for the development, manufacturing, and approval of biotherapeutics, which are often more stringent than those for traditional small-molecule drugs.

Regulatory pathways: The regulatory pathways for biotherapeutics can be complex and time-consuming, as they involve multiple stages of preclinical and clinical development, as well as post-marketing surveillance. Some of the key aspects of the regulatory process include:

1. **Preclinical development:** This stage involves extensive laboratory and animal testing to evaluate the safety, efficacy, and pharmacokinetics of the biotherapeutic candidate. Regulatory agencies require comprehensive data from these studies before granting approval for clinical trials in humans. This phase of development of the molecule can take 5-8 years.

2. **Clinical development:** Clinical trials are conducted in multiple phases (Phase I, II, and III) to assess the safety, efficacy, and optimal dosing of the biotherapeutic in humans. These trials must adhere to strict guidelines and protocols, comply with Good Clinical Practices (GCP) and their results are closely scrutinized by regulatory agencies. Depending on the indication the biologic is being developed for, clinical trials can be very extensive and time consuming. This also is the costliest stage of the life cycle of the molecule**.**

3. **Marketing authorization:** Upon successful completion of clinical trials, the developer/sponsor submits a marketing authorization application (MAA) or biologics license application (BLA) to the relevant regulatory agency. This application includes extensive data on the biotherapeutic's safety, efficacy, manufacturing process, and quality control measures. The agency then reviews the application and decides whether to approve the biotherapeutic for marketing and distribution.

4. **Post-marketing surveillance:** Once a biotherapeutic is approved and available on the market, the developer is required to conduct ongoing monitoring and reporting of its safety and efficacy. This may include post-marketing studies, adverse event reporting, and periodic safety update reports.

Key CMC challenges and strategies: Chemistry, Manufacturing, and Controls (CMC) is a critical aspect of the regulatory process for biotherapeutics[8], and includes:

1. Product heterogeneity-characterization and analytical methods: Biotherapeutics are inherently heterogeneous and more complex than small-molecule drugs because of their structure and post-translational modifications. This can make their development, manufacturing, and regulatory approval processes more challenging and time consuming. Strategies to address product heterogeneity include the use of advanced analytical techniques and the implementation of robust process controls.

The emergence of biosimilars, which are highly similar but not identical versions of approved biotherapeutics, has introduced additional regulatory considerations and guidelines for demonstrating their safety, efficacy, and interchangeability with the reference product.

Characterization of biotherapeutics involves the identification and quantification of their critical quality attributes (CQAs). Analytical methods must be developed and validated to ensure the accurate measurement of these CQAs. These methods include techniques such as mass spectrometry, chromatography, and immunoassays.

2. Manufacturing process variability- process development and validation: Manufacturing processes for biotherapeutics can be highly variable due to the use of living organisms as production systems. Strategies to address process variability include the implementation of process analytical technology (PAT) and the use of quality by design (QbD) principles. Process development is the optimization of manufacturing processes to ensure consistent production of biotherapeutics with the desired quality attributes. Process validation is required to demonstrate that the manufacturing process consistently produces a product that meets its predetermined specifications and quality attributes.

3. Stability studies: Stability studies are conducted to determine the shelf life and storage conditions of biotherapeutics. These studies help to establish the expiration dating and appropriate storage conditions for the product during conduct of clinical trials and after approval when they are in the market.

4. Comparability studies: Comparability studies are required when changes are made to the manufacturing process, such as changes in scale, equipment, or manufacturing site. These studies are designed to demonstrate that the product remains comparable in terms of quality, safety, and efficacy before and after the change.

5. Global regulatory harmonization: Differences in regulatory requirements between countries can present challenges for the global development and approval of biotherapeuticsand developers must navigate the varying regulatory requirements and guidelines of different countries and regions. Strategies to address regulatory harmonization include engaging with regulatory agencies early in the development process and participating in international harmonization initiatives.

DISCUSSION AND CONCLUSION

Due to the complex nature of biotherapeutics and the fact that they are produced in living organisms, makes the production of these drugs difficult, costly and time consuming. The heterogeneity of biologic drugs and the multiple steps used for their manufacturing & purification, warrants that the processes used should be robust to consistently make the product of desired quality that meets the present acceptance criteria. To help reduce batch to batch variability, achieve consistency in the manufacturing process and ensure the highest quality of the drug product, the guidelines established by regulatory agencies should be implemented by the drug developer. CMC regulatory considerations, compliance with guide lines and strategies to overcome the challengesare of utmost importance to provide the complete benefit of the drug to patients in need.

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