



Biosimilar Drug Development and Approval Process

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Abstract

The U.S. Food and Drug Administration (FDA) is responsible for advancing the public health by helping to review and evaluate biosimilar innovations that make medicines safer and more effective and by helping the public get the accurate, science-based information it needs to use medicines to maintain and improve public health. This presentation emphasizes quality system approaches to the development and availability of new drug information presented in the premarket applications. For approvals of biosimilars, the sponsors of premarket applications must present analytical characterization, pharmacokinetic (PK) and pharmacodynamic (PD) profiles, and comparative clinical studies to demonstrate that a proposed biosimilar is highly similar to a licensed reference product. It is recommended that a proposed bio similar product be tested for intended clinical use described in the licensed reference product's labeling. The protocol requires a sponsor to describe the bio similar product's PK/PD clinical data comparing its safety, efficacy, and immunogenicity to that of the reference product. FDA reviews clinical safety and efficacy of the biosimilar product and it is essential that any residual risks and hazards are mitigated to acceptable levels. FDA emphasizes the quality system approach to design and development studies by ensuring that organized data and appropriate labeling are presented in support of the new biosimilar's intended clinical use. Emphasis is placed on quality-by-design (QbD) approach to design of studies by providing guidances for analysis and expected clinical PK/PD data for the use of biosimilars in appropriate patient population studies. FDA field investigators evaluate the biosimilar product's c-GMP risk-based requirements and make recommendations based on whether the manufacturer has the required checks and balances in place and whether the manufacturer verifies and validates the implementation of critical quality attributes (CQAs) of the proposed biosimilar product. Biosimilar applications are approved based on totality of evidence described in U.S. FDA guidance documents.

Keywords: Drug administration; Pharmacodynamic; Immunoglobulin

Introduction

The U.S. Food and Drug Administration (FDA) is responsible for advancing the public health by helping to speed innovations that make medicines safer and more effective and by helping the public get the accurate, science-based information it needs to use medicines to maintain and improve public health. This publication provides an

overview of biosimilar products development and evaluation criteria for FDA approval. FDA provided a general guidance document for innovations, challenges, and solutions for new drug products that examine the critical path needed to bring therapeutic products to completion, and how FDA can collaborate in the process, from laboratory to production to end use, to make medical breakthroughs available to those in need as quickly as possible [1,2].

In new drug clinical applications, quality-by-design (QbD) approach is one of the most important features, while sponsor's drug product development team deals with the formulation, manufacturing processes, container closure features, and user instructions [3-5]. FDA requires a biosimilar product to be similar, but not identical to the existing biologic medicine (referred to as a "reference product") [6-8]. As more biosimilar products are developed, it is imperative that pharmaceutical companies develop strategies to comply with evolving regulations, mitigate risks, and implement requirements for their clinical applications. FDA guidance help sponsors of new biosimilar drug products in terms of providing organized data and appropriate labeling information in support of the new biosimilar drug's clinical use, development, and approval process [8].

Biologics

Biological products are generally derived from living materials--human, animal, or microorganisms. Biological products are large complex molecules in comparison to chemically synthesized small molecular weight generic drugs. Section 351 of the PHS Act defines a "biological product as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component, or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings". Biological products subject to the PHS Act also meets the definition of drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act). In terms of structure differences, biologics are large molecules, and cannot be described efficiently with a precise formula in contrast to chemically synthesized small molecular weight drugs, which have a well-defined structure and can be thoroughly characterized.

Furthermore, changes in the manufacturing process, equipment, or facilities could result in changes in the biological product itself and sometimes require additional clinical studies to demonstrate the product's identity, purity, potency and safety. In contrast, traditional drug products usually consist of pure chemical substances that are easily analyzed during manufacturing processes [1-5]. These fundamental differences in complexity and large scale manufacturing are at the core of why biosimilars are not equal to generic drugs; therefore, these differences require biological products to follow the broad regulatory steps for approvals. There are preclinical and clinical studies, and finally appropriate manufacturing adjustments, using c-GMP requirements that require biologics to have an investigational new drug (IND). The matrices of biological products are unique and complex and; therefore, require a drug product development section of an NDA containing information on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage protocol are appropriate for the intended purpose specified in the NDA.

Any parameters relevant to the performance characteristics or manufacturability (i.e., active ingredients, release testing, stability, etc.)

are addressed in the NDA [3,5]. Biologics are unique and complex molecules. Biologics are produced in living cells with multistep processes, extracted and purified in comparison to small molecular generic drugs manufactured via chemical synthesis. In regard to these major structural and manufacturing differences, regulatory guidances have outlined robust data requirements to demonstrate similarity to reference biologics. Biosimilar applicant sponsors generally need to generate data from lab testing, non-clinical, and clinical data in order to show that the biosimilar they have developed will provide the same therapeutic benefit and risks to patients as the reference product [2,7,8].

Biologics Approval Process

The sponsor of products of biological origin submits a biologics license application (BLA) under Title 21, CFR, Parts 314 and 601 (FDA forms 356(h)). The BLA consists of reports of all studies sponsored by the applicant, along with other pertinent information for the evaluation of the product's purity, potency, safety, and effectiveness. Even though the basic framework of chemical drug development applies to small drug molecules, it also applies to biological products including blood-derived products, vaccines, *in vivo* diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products. Biological products subject to PHS Act also meets the definition of drugs under FD&C Act.

The development process approach for a biologic product is essentially the same as that for a traditional small molecular drug. This is based on a systematic approach to structure and function of the small drug molecule studies relative to expected clinical outcomes. In these situations, studies may be based on high throughput screening using enzyme immunoassays. For example, it may be cloning a specific antibody and demonstrating *in vitro* studies as it binds to its ligand. In those situations where sufficient evidence exists, additional studies may be required. These studies, along with supporting manufacturing data including process controls, analytical methods, nonclinical, and clinical data are assembled into IND application [4].

Analytical methods may be referred to different types of *in vitro* assays addressing characterization of the active drug molecule and *in vivo* testing of drug levels and/or biological outcomes. For instance, a change in the fermentation process for the growth of production cells may lead to the introduction of new/modified species of the protein of interest (i.e., a new glycoform). In these types of situations, a detailed analytical characterization of the new/modified process-derived materials could go undetected by routine release testing methodologies ending up in novel immunogens as end-products [2,3]. The regulatory requirements for chemistry, manufacturing, and controls (CMC) may address some of the elements described above [1-5].

The CMC manufacturing section requires biologics product's batch record representing drug's substances production process which provides information in two key areas: (1) In-process controls and (2) process validation. This includes a description of the methods used for in process controls (i.e., those involved in fermentation, harvesting, and down-stream processing). For testing performed at significant Critical Control Points (CCP) phases of production, criteria for accepting or rejecting are provided. In those situations where process is changed or scaled up for commercial production and this involves changes in the fermentation steps, a revalidation of cell line stability during growth is described and the data and results are provided. A

description and documentation of the validation studies for the cell growth and harvesting process that identifies CCP parameters of process validation are provided [4,5]. Also, description and documentation of the validation of the purification process is included in the manufacturing process [3,4].

In those situations where reference standards are used (i.e. WHO, USP), the sponsor of the biologics application is required to identify and submit the citation for the standard and a certificate of analysis. If an in-house working reference standard is used, a description of the source, preparation, characterization, specifications, testing protocol and results are provided [3,5]. The specifications and tests to assure the identity, purity, strength, potency, and the stability of the drug substance, as well as its lot-to-lot consistency, are provided in the application.

The sponsor includes any impurities and analytical studies of the drug substance and information on container and closure system and its compatibility with the drug substance. This section includes information in regard to supply chain's profiles of tests, toxicity and compatibility studies. This information can be referenced in the drug master file (DMF). In regard to methods of manufacturing, a complete description of the process controls of the drug product's sterilization, aseptic and packaging procedures are described. This section includes a flow diagram indicating each CCP step [1-5].

Biosimilars

Biosimilar drug products are not considered chemically identical to their originator products because of structural differences of biosimilar molecules. For approvals of biosimilars, the sponsors of 351(k) applications must present analytical characterization, pharmacokinetic and pharmacodynamic profiles, and comparative clinical studies to eliminate any residual uncertainty. In order to show that a proposed biosimilar is highly similar to a licensed reference product, the sponsor submits analytical studies demonstrating similarity to the reference product, animal studies (including toxicity assessment), and one or more studies in at least one clinical indication for use to demonstrate purity, potency, and safety of the proposed biosimilar (Figure 1) [7,8]. It is imperative for the proposed biosimilar to be tested for one of the intended clinical use described in the licensed reference product's labeling.

The protocol requires a sponsor to describe the biosimilar candidate in a PK/PD study including healthy volunteers and clinical study comparing its safety, efficacy, and immunogenicity to that of the reference product in one of the clinical indications for use (Figure 2). Biosimilar products are evaluated by demonstrating similarity to the reference product via Totality of Evidence (Figure 3). The FDA approval process consists of analytical comparison, biological characterization, preclinical and clinical studies to evaluate PK/PD and safety data presented in the sponsor's 351(k) application (Table 1).

Biosimilars Approval Process

The biosimilar approval process provides a thorough characterization of the molecular structure related to safety and efficacy of the proposed biosimilar product and clinically meaningful data. The most prominent development and application concepts are:

Design Controls, validation and verification studies (Analytical Similarity, Manufacturing and Effective CMC Strategy)

QbD approach to Biosimilar Development and Applications [2-8]

Statistical considerations for demonstration of analytical similarity [7]

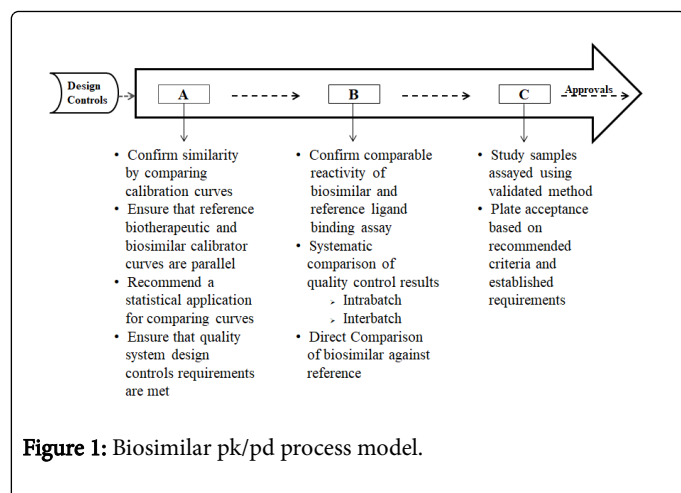
Clinical aspects of proposed biosimilar product (Design of studies, Immunogenicity Assessment, Extrapolations and Interchangeability) [2-12]

FDA Guidance on Biosimilar Labeling (Conformance with specific recommendations for labeling for interchangeable biological products) [8-12].

Discussion

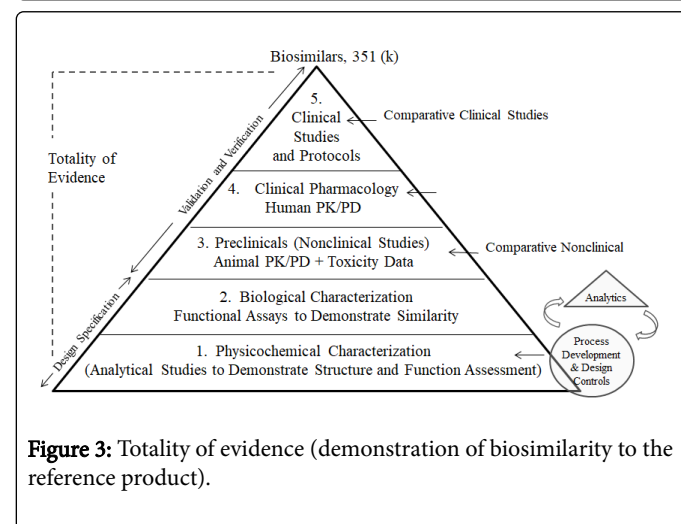
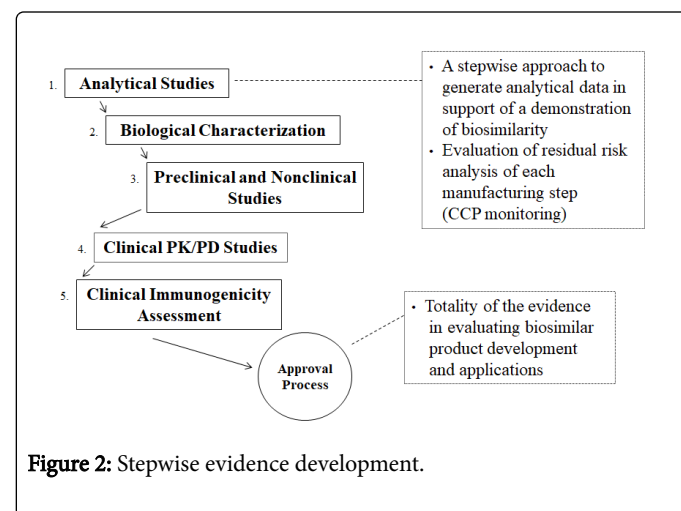
One of the most integral features of biosimilar development is the analytical characterization of significant lots of the innovator product and the proposed biosimilar product (Figures 1-3). These characterization studies show that primary amino acid sequence, tertiary structure specificity, and the mechanism of actions of biosimilar and innovator drugs are similar under Design Controls requirements of the FDA's CGMP/QbD guidances [4,6]. The International Conference on Harmonization (ICH) defines QbD as a systematic approach to development that incorporates the predefined objectives and emphasizes products's process controls based on quality risk management (ICH 2009) [6].

The goal of this requirement is to ensure that built-in quality of the product from its design prototype phase through manufacturing and post-marketing surveillance is maintained. The basic element of QbD requirement is Quality Attributes of Product Profile (QAPP). This entails quality characteristics of the biosimilar product which addresses the design of dosage form, strength, route of administration, intended clinical indication, safety and efficacy. This element also includes the product's quality criteria for the intended clinical use in terms of purity, stability, potency and safety. The QAPP is also known as critical quality attributes (CQAs). The CQA under ICH 2009 is also considered as a physical, chemical, biological, or microbiological characteristic feature of the output of the material including finished biosimilar drug product that should be within designed appropriate limits, range, or distribution for intended clinical use described in the labeling of the approved product [6-10]. Risk analysis and monitoring are described in ICH Q8 and Q10 documents [4-6,10].



ICH Q8 (ICH 2009) describes the design space related to manufacturing process inputs, which includes both the CQA of the drug materials as well as CCPs design specifications, validation and

verification of biosimilar products (Figure 3). The design space is described as the relationship between CQA of the product and process input/output. The design space for biosimilars is based on evaluation of the reference product, which is related to consistent quality improvement standards applicable to product quality (ICH 2009, 2012) [4,6,8]. This quality control strategy is derived from current product and process controls monitoring through the implementation of Process Analytical Technology (PAT) and HACCP Quality Monitoring System [2-6]. These quality control strategies help enhance the consistency and coordination of FDA's drug quality management programs. The ICH Q9 and Q10 were adopted by the U.S. in 2009 [4-6]. FDA guidance, "Quality Systems Approach to Pharmaceutical cGMPs" describes the main purpose to help sponsors of new medicines management tools to meet the requirements of the agency's cGMPs. The implementation of ICH Q10 throughout the total product life cycle (TPLC) strengthens the link between drug development and manufacturing processes (Figures 1-3) [6-8].



Extrapolation

One of the advantages under biosimilar 351(k) pathway is the term "extrapolation," which means that the sponsor need not conduct extensive clinical studies to cover every clinical indication for use described in the reference product labeling. However, the sponsor

usually conducts clinical evaluations in one or two indications for use described in the reference product's labeling and provides scientific rationale for extrapolating clinical data in support of biosimilarity [7,8,11].

The major concept of extrapolation is based on scientific rationale provided by the sponsor indicating that protein structure plays a key role in demonstrating the specificity of the protein structure related to performance characteristics of the biosimilar product and ultimately PK/PD, safety and efficacy of the proposed biosimilar product [10]. Based on the scientific rationale, the key elements of extrapolation include (mitigation of residual uncertainty/acceptance of minimal functional differences between the proposed biosimilar and the reference products (Figures 1-3) (Table 1) [6-8].

The sponsor of biosimilar product provides justification that mechanism of action in each indication does not produce any residual

uncertainty or hazards giving any significant differences in clinical safety and efficacy due to extrapolation. This justification includes safety and immunogenicity profiles that clinical safety will not be affected by extrapolation (Figures 2 and 3) [2-6,11].

It is important to clarify that extrapolation does not represent multiplicity of indications presented in the reference product's labeling, but instead this part of regulation represents structural-functional similarity and the scientific basis of how the biosimilar product's physical-chemical functional data represents structural-functional similarity to licensed reference product's mechanism(s) of action (MOAs) and the proposed biosimilar product represents highly similar to the reference product.

	Regulatory requirements	Applicant's biosimilar data requirements
Regulatory demonstration of similarity	•Analytical studies	•Physicochemical and functional analytical data demonstrating that biosimilar product is highly similar to US licensed product
	•Nonclinical studies	•Animal studies (comparison and confirmation showing the pharmacologic and toxicological profiles of candidate biosimilar and reference product)
	•Clinical studies	•Clinical studies to evaluate PK, PD and safety studies
Clinical demonstration of similarity based on reference biologic studies	•Mechanism of action (Receptor binding assays)	•Selective binding to the G-CSF receptor and showing similarity across all indications for use described in the labeling
	•Route of administration(Dosage form and strength in comparison to US licensed reference product)	• Candidate biosimilar product dosage form and strength as US licensed reference product

Table 1: Biosimilar essentials for approvals.

According to FDA's guidance for industry the MOAs in each indication for use may include:

The target receptor(s) for each relevant (activity/function) of the proposed biosimilar product (Figures 1 and 2)

The receptor binding, dose-concentration response, and output signal(s)

The mechanisms between biosimilar product's structure (target/receptor stereochemical interactions)

The location and outputs of the target/receptors

The PK and distribution of the biosimilar product's applications in different patient populations

The immunogenicity assessment of the proposed biosimilar in different populations

Comparative differences in toxicity profiles under each indication for use

Factors that may affect the safety/efficacy of the proposed biosimilar in each indication for use

FDA guidance indicates that differences between conditions of use in regard to factors listed above do not necessarily preclude extrapolation. FDA requires "totality of evidence" in regard to extrapolation as long as it is based on scientific rationale and

justifications. The guidance also recommends that proposed biosimilar sponsor conduct clinical studies in a condition of use that would be adequate to detect clinically meaningful differences between the candidate biosimilar and reference product [8]. The concept of extrapolation depends on the basis of biosimilar drug molecule being highly similar to the licensed reference product and the mechanisms of action in treatments are according to reference product's indications for use.

Interchangeability

The concept of interchangeability or switching is based on the criteria of switch from the reference product to the biosimilar. It is important to distinguish between the single switch and multiple switches between the reference product and a biosimilar. Section 351(k)(4) of the PHS Act determines the criteria for demonstrating interchangeability of the biosimilar with its reference product [12]. In this guidance, it is stated that "biosimilar product can be expected to produce the same clinical result as the reference product in any given patient."Section 351(i) of the PHS Act also indicates that "any biosimilar that meets the requirements described in this section for interchangeability may be substituted for the reference product". In order to be considered for the substitution, FDA requires that candidate biosimilar must undergo additional testing and clinical studies (Figure 1 and Table 1). Additionally, FDA requires the post-marketing vigilance data for the new biosimilars – particularly those

with more complex molecular structures. It is expected that “stepwise evidence-based development” provides a more sensitive PK/PD information/data, on a case-by-case basis along with switching studies to demonstrate interchangeability (Figure 2) [6-12].

Conclusion

FDA field investigators evaluate the biosimilar product's c-GMP risk-based requirements and make recommendations based on whether the manufacturer has the required checks and balances in place, and whether the manufacturer verifies and validates the implementation of critical quality attributes of the proposed biosimilar product. FDA reviews clinical safety and efficacy of the biosimilar product and it is essential that any residual risks and hazards are mitigated to acceptable levels. FDA emphasizes the quality system approach to design and development studies by ensuring that organized data and appropriate labeling are presented in support of the new biosimilar's clinical use. The emphasis is placed on QbD approach to design of studies by providing guidances for analysis and expected clinical PK/PD data for the use of biosimilars in appropriate patient population studies. Biosimilar applications are approved based on totality of evidence described in U.S. FDA guidance documents.

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