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Development of biosimilars

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ABSTRACT

Objective: To provide an overview of the underlying scientific principles and standards for developing a biosimilar product.
Methods: An Internet-based literature search through June 2015 was performed for information related to biosimilar manufacturing and development, including a review of regulatory guidelines and requirements.
Results: Biologics, both biosimilars and their corresponding reference products, are complex molecules produced by biotechnology in living systems. The development of biologics involves multiple levels of intricate, highly controlled manufacturing processes, combined with pre-clinical structural, functional, and biological assessments, as well as clinical efficacy and safety, including immunogenicity, analyses. In addition, to ensure a high degree of similarity, a biosimilar must undergo a comparability exercise at every step of its development, as outlined by regulatory agencies, to demonstrate that potential differences from the reference product are not clinically meaningful with regard to quality, safety, and efficacy [European Medicines Agency (EMA)] or safety, purity, and potency [US Food and Drug Administration (FDA)]. At the foundation of the biosimilar development process lays the establishment of a high degree of structural similarity with its reference product. State-of-the-art technologies must be employed to demonstrate a high degree of structural and functional similarity. Finally, clinical pharmacokinetic and pharmacodynamic as well as clinical efficacy and safety similarity must be confirmed between biosimilar and originator. Regulators, including the FDA and the EMA consider the totality of the evidence from this comprehensive step-wise comparative similarity exercise in its determination of biosimilarity for licensing.
Conclusions: The rigorous and highly regulated processes required to develop a biosimilar have been designed as such to establish a high degree of biosimilarity with a reference product in terms of the structural, functional, biological, and clinical attributes.

Introduction

Available in the European markets for almost a decade, biosimilars are becoming more readily accessible worldwide, as various biologic drugs lose patent protection and new regulatory pathways are implemented [1]. The European Medicines Agency (EMA) has approved multiple biosimilars, including the first monoclonal antibody (mAb) biosimilars for infliximab (Remsima and Inflectra) in 2013 [2]. In the United States, the requirements for the approval and license of biosimilars are specified in Section 351(k) of the Public Health Service Act. Through the pathway established in Section 351 (k), biosimilar licensing relies, in part, upon the extensive knowledge gained with the originator (or reference) product, allowing for an abbreviated clinical data package [3]. In the United States, the first biosimilar, filgrastim, was recently approved through this pathway [4].

Because biologics are complex molecules that are produced through manufacturing processes in living cells, biosimilars cannot be characterized to a level typically possible for small molecules. There has long been an awareness that small differences in

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clinically meaningful molecular attributes in biologic products may have clinical consequences. Specific scientific and regulatory approaches are required that ensure biosimilars meet the high degree of similarity necessary to reflect the safety and efficacy of reference products [5]. To this effect, regulators have issued guidance documents that are continuously updated and refined, as described in the previous article, "Biosimilars: Rationale and Current Regulatory Landscape," in this supplement [6].

Before prescribing a biosimilar, it is critical that clinicians understand the totality of evidence supporting its biosimilarity to the reference product and the fundamental criteria that must be met for a biotherapeutic to be labeled a biosimilar product [7].

Biopharmaceutical manufacturing

The manufacturing processes used to produce biopharmaceuticals, including both biosimilars and originator biologics (also known as novel or innovator products), involve specialized, expensive, and time-consuming operations [1,8,9]. Biopharmaceuticals are large-molecule medicines manufactured biologically, rather than chemically, using a living cell line cultured under well-controlled conditions. The predecessor to routine biologic manufacturing is the production of a cell line containing the gene that makes the desired protein in sufficient amounts and with the desired post-translational modifications. During the routine manufacturing process of a biologic, there are three main steps: (1) cell expansion and expression, (2) protein isolation and purification, and (3) formulation and drug product packaging for patient use (Figure) [9–11]. Manufacturing processes are constantly improving, with the bioprocessing methods and systems continuing to increase efficiency, productivity, and product safety/quality [12]. Improvements, including single-use bioprocessing systems and modular bioprocessing facilities, are increasingly making bioprocessing more attainable [13].

The manufacturing process must be well controlled, as small changes in manufacturing processes may have a large impact on the final product's efficacy and safety, including immunogenicity [8,14]. Glycosylation, for example, can be critical for the biological function of mAbs [15], and product-related substances or impurities such as deamidated, isomerized, and oxidized forms, or protein aggregates that may develop during production or product storage can also affect both the structure and the antigen-binding properties of mAbs [16]. As such, processes are strictly controlled and monitored to achieve consistent product quality of all attributes, including primary structure, higher-order structure or conformation, and post-translational modifications [8]. As a result, an in-depth understanding of the product and manufacturing process, as well as highly specialized equipment, are required [17].

Because of their impact on the safety and quality of therapeutics, including biologics, drug manufacturing processes are highly regulated [14]. Appropriate manufacturing controls are expected by regulators based upon scientific and risk management principles. The first initiative for the risk-based approach for current good manufacturing practices (cGMPs) was introduced in 2002 by the US Food and Drug Administration (FDA) [18,19]. The overall aim was, and continues to be, to ensure strong public health protection through risk management, science-based policies and

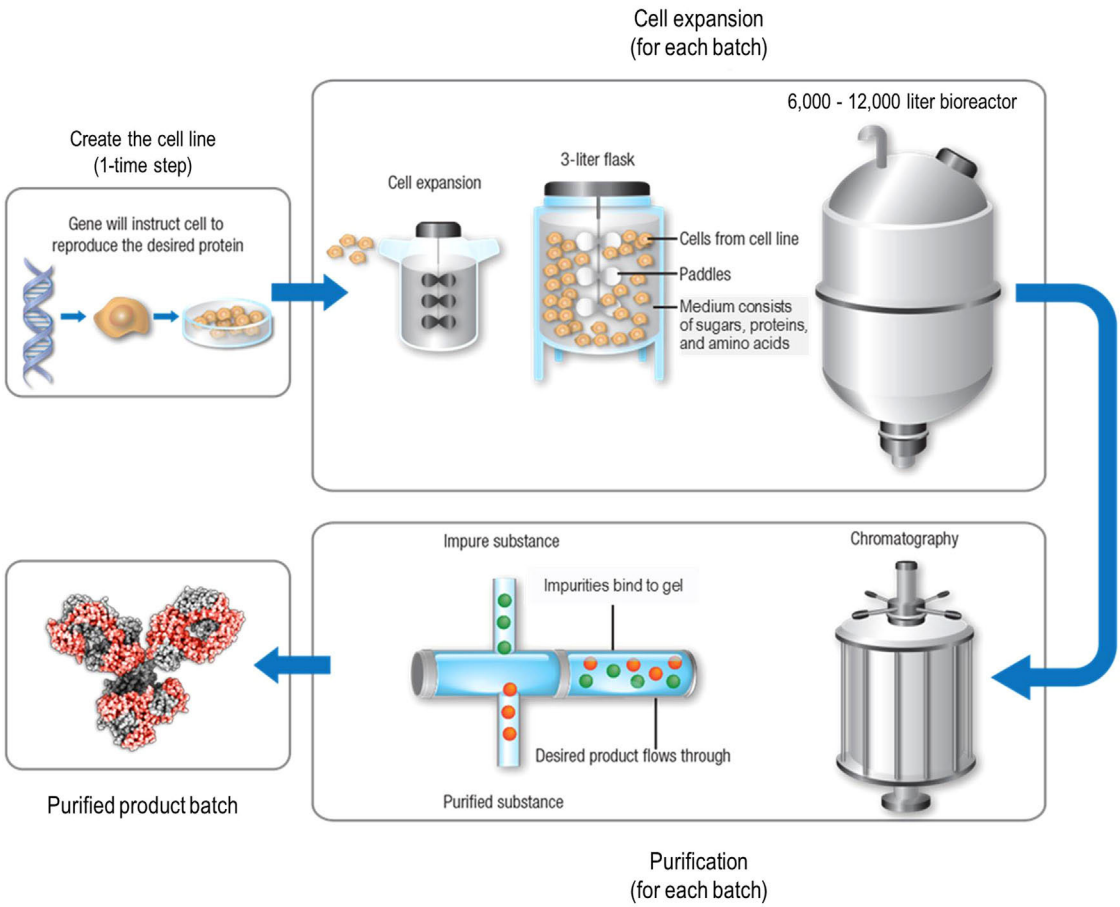

Fig. The development and manufacturing processes to produce and purify biopharmaceuticals, both biosimilars and novel biologics, involve well-controlled, complex operations [10].

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