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Introduction

Recombinant DNA-derived biopharmaceuticals are structurally complex proteins derived from genetically modified living cells or organisms that are difficult to characterize. Because of inherent variability in the biological system and the manufacturing process, any biologic will exhibit microheterogeneity—that is, there will be a certain degree of variability even between different batches of the same product. Several biological products have lost patent protection in recent years, particularly in Europe and to a lesser extent (but soon to change) in the United States (US). This, in turn, has created significant clinical and economic opportunities for pharmaceutical companies to develop and seek marketing authorization for a number of biopharmaceuticals (e.g., human growth hormone, erythropoiesis-stimulating agents [ESAs], granulocyte colony-stimulating factors [GCSFs])—and in the not-so-distant future, insulin, interferon β, recombinant follicle stimulating hormone and various monoclonal antibodies.1-3

Drawing upon our work on the clinical efficacy and safety of biosimilar recombinant human erythropoietin4-8 and filgrastim, 9-11 as evidenced in registration trials and post-approval studies, we review here three issues of relevance to the bioengineering field: (1) definition, (2) development and (3) differentiation of biosimilars. For the purpose of this article, we limit the scope to biosimilar ESAs and GCSFs already approved by the European Medicines Agency (EMA) because, to date, the US Food and Drug Administration (FDA) has not approved a biological product as biosimilar or interchangeable. A few product reviews have been accepted under the FDA’s conventional Biologics License Application (BLA) pathway, including the GCSF Tbo-filgrastim, which is the same agent as XM02 approved by the EMA. Epoetin theta was approved by the EMA as a stand-alone product. It is technically not considered a biosimilar by some12 but is practically and clinically viewed by others as such.13 There are biosimilars produced in less regulated markets; however, they are not considered in this article.

Definition: Not a Generic but a Unique Protein

Though it is tempting to analogize biosimilars to generics, biosimilars are not “copy” versions of biological therapeutic agents. According to the FDA, a generic drug is a drug product that is “identical”—or bioequivalent—to a brand name drug in dosage form, strength, route of administration, quality and performance characteristics and intended use.14 Similarly, the EMA defines a generic drug as “a medicine that contains the same active substances as the reference medicine,” and it is “used at the same doses to treat the same diseases.”15 Biosimilars, on the other hand, have very different definitions. The EMA defines a biosimilar as “a biological medicine that is similar to another biological medicine that has already been authorized for use.”16 The FDA uses the term biosimilar to describe...
“a biological product that is highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar and the approved biological product in terms of the safety, purity and potency.”

In essence, a generic drug is an exact replacement of a reference product, quantitatively and in terms of its bioavailability and bioequivalence. Biosimilars differ from generics in terms of the complexity of the active substances, their microheterogeneity as finished products, their starting materials and the genetically modified living cells or organisms used and the production and purification processes. The manufacturing process is complex, consisting of choice of cell type, production, purification and formulation. Hence, a biosimilar will never be the same as the reference product, only similar—and, preferably, as similar as possible.

Biosimilars are variations of the complex threedimensional (3D) structure of the reference product. Structural analysis identifies the primary structure of a reference product, but also the secondary and tertiary structures—possibly even the quaternary structure. These structures can be mimicked, and they may alter some properties of a biological, such as duration of the action and the activity. The complexity of biological molecules further complicates the identification of biosimilar candidate molecules. Increasing complexity translates into a greater number of possible variations. This makes it virtually impossible to physicochemically characterize each potential molecule vast. By necessity, the search for a quality biosimilar candidate should target candidate molecules that meet (narrow) physiochemical quality parameters.

Even after good molecule candidates have been identified, the manufacturing process influences their quality, purity, biological parameters and clinical activity—all of which determine its clinical efficacy and safety. In fact, in the biologicals and biosimilars space, it is often said that the product is the process—that is, the biopharmaceutical is determined by the process by which it was produced.

Schellekens, who perhaps has substance vested in the most to the biosimilars debate (and a judicious advocate of biosimilars himself!), fairly cautioned that “even if the biosimilar product has the same gene sequence, vector, host cell line, culture conditions and purification method” as the originator product, “it can still differ substantially in its biological and clinical properties.” Therefore, each biosimilar, within its therapeutic class or across therapeutic classes, is considered a unique protein.

Pun intended, biosimilars are not immune to the problem of immunogenicity: the ability of virtually any protein, including a recombinant human protein, to elicit an immune response and the production of antibodies. Immunogenicity may be a potentially severe adverse event if the antibodies to the recombinant exogenous protein interact with (or both) the endogenous or exogenous proteins. In the best case, there will be no observable effect on either of these proteins. Alternately, the antibodies may bind to and attenuate or inactivate the endogenous protein, resulting in hypersensitivity reactions ranging from drug hypersensitivity to allergy and possibly anaphylactic reactions. In the worst case, the antibodies may neutralize the endogenous protein. More importantly, recent reviews of the clinical safety of the three biosimilar recombinant human erythropoietins and the three biosimilar recombinant GCSFs approved by the EMA (and one biosimilar G-CSF approved by the FDA though the conventional BLA pathway) found no differences in clinical safety profiles of these biosimilar agents relative to their originators in the respective classes.

Development: Straight-Up Pyramid

Figure 1 shows the drug development program of a biosimilar. The biosimilar development pyramid is based on the molecular analysis of many molecular candidates—all variations on the molecular structure of the originator product. Because of the number of potential variations in a complex biological molecule, this entails a lot of work and requires extensive resource commitments. The objective is to narrow this down to a defined set of candidate molecules. Subsequent biological analyses aim to separate out those molecules (or, ideally, one molecule) with the best physiochemical characterization—to take it into pre-clinical (animal) and clinical development. Phase I trials cover both pharmacokinetics and pharmacodynamics of the pharmacoepidemiology of immunogenicity remains limited and has been derived mainly from “surge” events (e.g., pure red cell aplasia due to neutralizing antibodies to exogenous ESAs). As we cautioned in our reviews of biosimilar growth factors, to enable broader safety signal detection of adverse events with a lower incidence rate than what could be detected in Phase III trials, follow-on observational studies and registries with larger samples and greater heterogeneity of patients, clinicians and centers are warranted. Also helpful may be safety analyses from drug safety databases, claims databases and electronic health records. Post-approval studies are an essential part of late-stage clinical development and thereby drive the expansion of pharmacovigilance.
similarity and (as) small (as possible) degree of dissimilarity to the reference originator—along with many parameters. Structural analysis and physiochemical characterization reflect the complexity of the biological molecule and the challenge of finding the biosimilar with structural variation that has the greatest physiochemical quality relative to the reference product. Manufacturing processes are an integral part of each biosimilar produced. As proteins, they carry the risk of immunogenicity reactions with impacts from the non-observable to the highly severe. In development, the focus is on applying extensive molecular and biological analysis to establish the molecule and take it into preclinical development and subsequently, in clinical development, into Phase I and Phase III trials.

In differentiation, the emphasis is on establishing manufacturing processes that (defensively) do not infringe on extant patents. Mainly, though, the emphasis in biosimilars is to offer equally effective and equally safe product alternatives that are cost-efficient. In turn, this may improve access to treatment with biological agents and reduce health care costs.

Circling back to the theme of this article, the relationship of biosimilars to their reference biological products is fundamentally different from the (much narrower) relationship of generics to small molecule chemical entities. We identified three dimensions of relevance to the bioengineering field.

In definition, the uniqueness of biosimilars is expressed at several levels. The legal definitions of biosimilars relative to generics delineate the functional distinctions between both. Whereas collectively generics are identical copies of a reference drug, each biosimilar is considered a unique protein with a high degree of similarity and (as) small (as possible) degree of dissimilarity to the reference originator—along with many parameters. Structural analysis and physiochemical characterization reflect the complexity of the biological molecule and the challenge of finding the biosimilar with structural variation that has the greatest physiochemical quality relative to the reference product. Manufacturing processes are an integral part of each biosimilar produced. As proteins, they carry the risk of immunogenicity reactions with impacts from the non-observable to the highly severe.

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