Biosimilars and the Pharmacist: A Review of the Legal and Regulatory Issues Part 1

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Summary

Biosimilars are a new and rapidly expanding area of drug therapy. An abbreviated FDA approval process has been established for biosimilars using a stepwise approach to demonstrate biosimilarity, and nine biosimilars have been approved in the US since 2015. Biosimilars are approved through a unique framework that emphasizes bioanalytic similarity to the originator drug first, with limited clinical studies done to resolve any residual uncertainty about similarity. Biosimilars use such varied and potentially unfamiliar concepts as totality of the evidence, residual uncertainty, immunogenicity, and switching studies. These drugs have the potential to reduce costs and increase access to beneficial biologic therapies. However, policy decisions on pharmacovigilance systems, record-keeping, naming conventions, and reimbursement are still shaping the use of biosimilars. Pharmacists will be responsible for ensuring appropriate implementation of these policies and monitoring the safety and effectiveness of biosimilar therapy in patients.

Conclusion

Scientific, legal, and regulatory issues will be important for ensuring safe and effective use of biosimilar drugs now and in the future. Pharmacists need to understand these issues to contribute to policy discussions, answer questions from patients and prescribers, and assure appropriate use of these important medications.

Keywords: biosimilar pharmaceuticals; biological products; drug substitution; postmarketing drug surveillance; generic drugs.

Introduction

Biosimilars are drugs that have the same properties and clinical effects as a reference biologic drug. In theory, the concept is similar to generic versions of brand-name small-molecule drugs. However, the nature and production process of biologic drugs is much more complex than that of small molecules, which complicates the approval process for biosimilars. The US Food and Drug Administration (FDA) has developed a regulatory pathway for biosimilars, allowing a shorter development and approval process than what is required for a new biologic. It utilizes a stepwise approach to analyzing the molecule, using a variety of studies and assessing the accumulated evidence to inform the approval for each drug. This regulatory path is relatively new and involves unique concepts including totality of the evidence, extrapolation, immunogenicity, and interchangeability. The market for biosimilars has grown rapidly in recent years, and this is likely to continue. Thus, pharmacists have an obligation to be well informed.

Basics of Biosimilars

Biosimilar drugs must be understood in the context of their reference products: biologics. The term biologic encompasses a wide variety of compounds used for the prevention and treatment of disease, from vaccines to blood products to engineered versions of human proteins.[1]

With small-molecule drugs, the placement of every atom is precisely known and can be identically reproduced, yielding structurally and functionally equivalent brand and generic versions.[1] In contrast, biologics are highly complex and anywhere from 200 to 1,000 times larger than small molecules.[2] Additionally, the activity of a protein drug is dependent on numerous levels of structure as well as post-translational modifications, which require precisely controlled manufacturing conditions. If changes are made to the manufacturing process of a biologic drug, the FDA requires that the manufacturer prove that these changes do not result in any meaningful changes in the product. The manufacturing is even more difficult with development of biosimilars, since the manufacturer does not have access to the proprietary processes used by the innovator company. All manufacturers are limited by current analytical technologies for detecting changes in drug formulations, which can sometimes lack precision.[1]

The concept of biosimilarity as defined by the FDA means "that the biological product is highly similar to the reference product notwithstanding minor differences in clinical inactive components and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[3] A biosimilar drug must be identical to its reference in mechanism of action, strength, dosage form, and route of administration. It also can only be approved for indications that the reference product has been approved for, though it need not seek approval for all of these indications.[4] All currently FDA-approved biosimilars are protein drugs, mostly monoclonal antibodies, and many future biosimilars are likely to fall into this category. As discussed, it is not reasonable to expect perfectly identical products from batch to batch of a single protein drug, let alone when comparing a biosimilar to its reference product. Thus, the goal of the biosimilar approval process is to ensure that any minor variations do not affect the safety and efficacy of the biosimilar drug.[1]

FDA Regulatory Process

Small molecules are regulated under section 505 of the federal Food, Drug, and Cosmetic Act (FDCA). To gain approval, manufacturers must submit a New Drug Application (NDA) to the FDA. In contrast, biologics are regulated under section 351 of the Public Health Service Act (PHSA) and require a Biologics Licensing Application (BLA) for approval. It is worth noting that the line between small molecule and biologic is not always very clear, and some drugs that would ordinarily be considered biologics have been approved under the FDCA.[5] A few examples are insulin, glucagon, and human growth hormone.[6]

For over 30 years, manufacturers of small-molecule drugs have been able to use two abbreviated approval pathways to bring generic drugs to market once their brand-name equivalents have exhausted their market exclusivity.

Until recently, there was not a corresponding pathway for biologic drugs. Any proposed biologic, regardless of comparability to a previously approved product, would have to submit a full BLA or, in selected cases, an NDA with the entire complement of analytical, animal, and human clinical data.[7] However, this changed with the enactment of the Biologics Price Competition and Innovation Act (BPCIA) of 2009. This act allows a sponsor to develop and market a biologic drug through an abbreviated pathway under section 351(k) of the PHSA by proving comparability to a previously approved reference biologic.[3] The BPCIA also established a grace period, lasting until March 2020, wherein applications for biosimilars may still be submitted via the Hatch-Waxman process instead of the BPCIA. After that date, the 351(k) pathway must be used.[4]

In terms of regulatory status, the BPCIA and the Hatch-Waxman act both have two levels of similarity that a follow-on product may achieve. Generic small-molecule drugs are categorized in the FDA Orange Book with an A rating, indicating bioequivalence and interchangeability, or a B rating, indicating only bioequivalence. A ratings are common among generic small molecules, and this has allowed the widespread substitution of these drugs for their more expensive brand equivalents at the pharmacy level.[4]

Biologic drugs are classified in the FDA purple book as biosimilar or interchangeable. The basic designation of biosimilar is comparable to a B rating, and this category encompasses all drugs approved through the abbreviated BPCIA pathway to date. The BPCIA also establishes a higher level of biosimilarity, known as interchangeability, which is comparable with an A rating. The potential for interchangeable biologics is just beginning to be explored, and there are currently no such products approved by the FDA.[4]

In some sense, biosimilars can be conceptually likened to generic small-molecule drugs. However, biosimilars are not generics, and there are key differences between these categories that are a common source of confusion. To reiterate, the structural nature and simple production of small-molecule drugs allows for an easier process of proving bioequivalence, and the FDA is generally satisfied with a standard complement of analytical data showing that the brand and generic drugs are identical. In contrast, the complexity of biologic drug structure and production makes this unrealistic and necessitates a different approach.

Biosimilar Analysis

The FDA emphasizes a stepwise approach to establish biosimilarity between a new product and its reference biologic (Figure 1). As data come in from initial analytic studies, the FDA works with the developer to identify areas of "residual uncertainty" about the biosimilarity of the proposed product. The need for and extent of subsequent studies is determined on a case-by-case basis, and the FDA has the final say on what is required. It is important to note that the goal of these studies is not to "independently establish the safety and efficacy of the proposed product,"[1] since this has already been extensively studied for the reference product. Rather, the proposed biosimilar must prove that it has no clinically meaningful differences from the reference product.[1]

The first step is structural and functional characterization of the proposed product and its reference. This involves sensitive comparative analysis of the structures of the compounds, as well as assessment of batch-to-batch variation and evaluation of pharmacological activity. These assays are an important foundation for demonstrating biosimilarity, and strong data can reduce the requirements for subsequent studies.[1]

The next step is animal studies to assess toxicity of the proposed products, including general safety concerns, fetal risk, and carcinogenic toxicity. These are conducted based on the extent of data from previous studies and may not be necessary in some cases. However, they can be useful if there is uncertainty regarding the drug's pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity.[1]

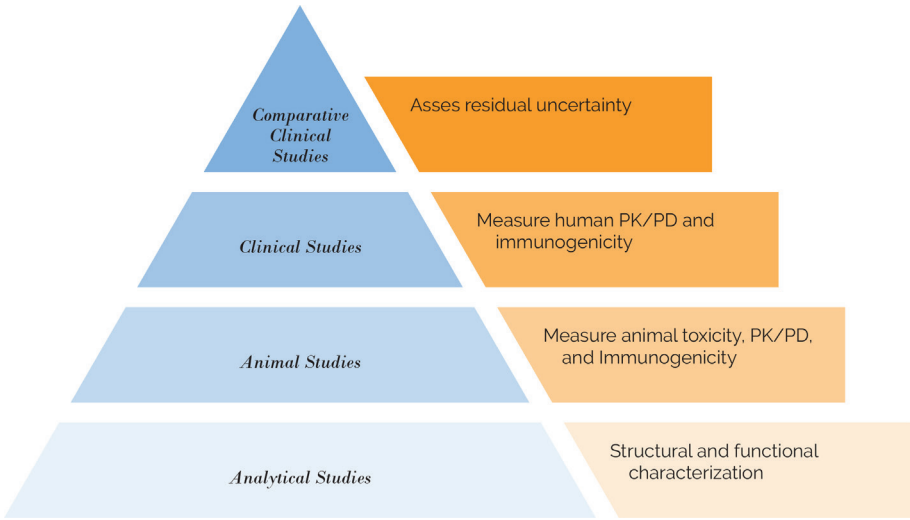
Finally, the FDA may require clinical studies to eliminate any residual uncertainty about the comparability between the proposed and reference products. Human PK and PD are not the same as in animals, so data on these are usually required. Likewise, assessing the immunogenicity of a biosimilar product generally requires human studies. This parameter is unique to biologic drugs and will be discussed in more detail below. Based on the results of these studies, the FDA will determine the need for comparative clinical studies that directly assess any remaining doubt of the biosimilarity of the products in question.[1] The FDA encourages drug sponsors to conduct their studies with doses, patient populations, and endpoints that are as sensitive as possible for detecting differences between the products in questions.[3]

The need for continued safety monitoring for a biosimilar drug after its approval is, as with other aspects of the process, variable and situationally determined. In reviewing the proposed biosimilar application, the FDA will determine the need for and extent of additional post-marketing studies.

The FDA looks at the totality of the evidence when evaluating proposed biosimilars.[1] This means that data is considered from all the studies enumerated above to inform the FDA's final decision on a product. As mentioned before, the presence of small variations between the proposed product and the reference does not mean that the former cannot be approved as a biosimilar. However, the drug's sponsors must prove in subsequent studies that they do not result in clinically meaningful differences from the reference product.[1]

As a side note, it is important to realize that innovator biologics also undergo subtle changes over time due to frequent changes in the manufacturing process.[8] With each change, the manufacturer must show that the characteristics of the newly produced product are the same as the originally approved drug. Thus, the way the FDA looks at a biosimilar is similar to how it re-

Figure 1. The totality of evidence approach used by the FDA to approve a biosimilar. PK/PD = pharmacokinetics/pharmacodynamics.



views manufacturing changes for innovators.

Extrapolation

Extrapolation is an idea frequently encountered in discussions of biosimilarity. It refers to the approval of a biosimilar drug for the treatment of multiple indications for which the reference product was originally approved, without explicit clinical study of the biosimilar in each of those indications. The manufacturer must provide adequate evidence that this approach is justified, and data may only be extrapolated to indications approved for the reference product. As with biosimilars more generally, the FDA looks at the totality of the evidence in assessing the appropriateness of extrapolation.[1]

Different regulatory bodies have taken different approaches to the approval of individual drugs for extrapolated indications, and not all biosimilars have been approved for all their reference product's indications.[2] In the US, extrapolation of indications has been common for the biosimilars approved so far, though approval via extrapolation in one country does not automatically entail the same approach in another.[9]

There is much debate surrounding extrapolation. For biosimilars to offer financial benefits, there must be a way of reducing the costs of their development and production. Extrapolation is an important mechanism for this, since it reduces the number of indications that must be tested in clinical trials.[10] But some advocacy groups have raised concerns that it is dangerous to use drugs in populations for which they have not had extensive study or in which the mechanism of action is not well understood.[11]

A position statement on biosimilars from the American College of Rheumatology (ACR) urges restraint in the practice of extrapolation, noting that proving safety and efficacy in one disease state does not guarantee it in others. It also notes the difference between drug action in adults and children, and advocates judicious use of pediatric studies. The guidance stresses the need for physician autonomy in clinical decision-making, and warns against blindly following cost-driven policies without due consideration of patient factors.[12]

Nonetheless, since analytical and clinical pharmacology studies have already demonstrated similarity of the biosimilar to its innovator product, the FDA takes the position that clinical studies for every approved indication are not necessary.

Immunogenicity

A unique factor in the discussion of therapeutic protein drugs, both biologics and biosimilars, is immunogenicity. This term refers to the ability of these drugs to stimulate the human immune system to react against the drug. This can manifest in numerous ways, from asymptomatic production of antibodies to life-threatening anaphylaxis. The main immunological concern with biosimilars is the production of antibodies.

On exposure to a protein drug, the immune system may recognize it as foreign and produce anti-drug antibodies (ADAs) against it. This is especially true if the protein is produced in a cell other than a human one, and some products are more intrinsically immunogenic than others. Antibodies may affect drug clearance or directly block the drug's activity, in the case of neutralizing antibodies.[13] And subsequent administration of the same or a similar product may result in a toxic reaction or at least reduced effectiveness of the product over time.[7][14]

Current evidence from clinical studies does not suggest that immunogenicity is increased with the use of biosimilars. A 2017 review article looked at 53 switching studies between reference products and biosimilars. About half of these studies included information on immunogenicity, and generally there was no difference in incidence of adverse effects. There are still limited data on the subject, though. Many articles and organizations urge careful consideration of patient-specific factors when switching and only doing so for clinical reasons, not merely for cost savings.[15] This has added significance in the case of interchangeable biosimilars.

Interchangeability

Interchangeability is another aspect of biosimilar development that is surrounded by uncertainty. When the ACA established the pathway for abbreviated biosimilar approval in 2010 (the BPCIA), it also defined a more rigoror-

ous level of biosimilarity, which requires that "the proposed interchangeable product can be expected to produce the same clinical result as the reference product in any given patient."[16] This designation also requires that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such an alternation or switch."[16] The safety of switching is a commonly cited concern in regard to biosimilars, and several studies have recently been conducted to address this.[17][18]

For example, NOR-SWITCH is an important yearlong trial that was conducted in Norway to establish the noninferiority of switching patients from reference infliximab to the biosimilar CT-P13. NOR-SWITCH followed 482 patients being treated with infliximab, including individuals with each of its six approved indications. Half of these infliximab patients were switched to biosimilar infliximab, while the other half continued their current treatment with the reference product. The primary endpoint was disease worsening, and adverse effects and ADA levels were measured at each visit. Though the study was not large enough to confirm noninferiority for each disease state, in aggregate, biosimilar infliximab was shown to be equal in efficacy and safety to the reference product.[17] The biosimilar product in question, CT-P13, was approved by the FDA in 2016 and is marketed in the US as Inflectra or infliximab-dyyb.[19]

The FDA only released a draft guidance document for the industry on interchangeability in January 2017, which closed for comments in mid-June. This guidance details considerations for developers looking to demonstrate interchangeability. The FDA proposes a stepwise approach to amassing evidence of comparability, as discussed with demonstration of basic biosimilarity. Other considerations include product-specific factors such as structural complexity, risk of adverse effects, and level of clinical experience with the product in the US or other markets. The FDA also requires that packaging and delivery systems be designed such that the intended administrator may switch between reference and biosimilar products without supplemental training.[16]

The demonstration of interchangeability is unique in that the FDA emphasizes the importance of switching studies. These are designed to assess the effect of alternating exposure to two proposed interchangeable products and consist of at least two alternating intervals of treatment with each product. Consistent with the definition of interchangeability given above, this type of switching must be proven to not result in lower efficacy or higher incidence of adverse effects.[16] Others have also advocated for studies with multiple switches, since many alternating exposures to biosimilar products may increase the likelihood that patients will develop a detectable immune response.[20]

One study that implemented this sort of switching was the EGALITY study, a yearlong RCT conducted in Europe and South Africa to compare the efficacy, safety, and immunogenicity of a proposed etanercept biosimilar (GP2015) to Enbrel. EGALITY followed 526 patients with plaque psoriasis. Half the patients were assigned to each drug for the first 12 weeks and were then reassigned to either continue on their initial treatment or to undertake three switches between the drugs between week 12 and week 30. Each treatment period was six weeks, and at week 30, all patients continued on their current treatment until the end of the study. The results supported the biosimilarity of GP2015 to Enbrel in terms of efficacy, safety, and immunogenicity.[21] GP2015 was subsequently approved in the US under the trade name Erelzi.[19] This study is unique given the use of multiple switches between the two products, after which there was no observed decrease in efficacy or increase in ADA formation.

Since many biosimilar versions of biologic drugs are likely to become available in the coming years, it is crucial that the decision to switch among them is supported by adequate evidence of preserved safety and efficacy.[20] This is especially important with interchangeables, since they may be substituted for the reference product by the pharmacist without direction by the prescriber.[16]

The BPCIA has a unique provision that awards one year of exclusivity to the first sponsor of an interchangeable product over subsequent interchangeable products for the same biologic. Additionally, the ability of pharmacists to automatically substitute the interchangeable product will speed its adoption. Thus, interchangeability, though it entails additional approval requirements, has definite economic incentives.[4]

No interchangeables have been approved in the US to date, but the recent release of the FDA draft guidance and the associated economic benefits are likely to change that.

The Biologics Prescribers Collective (BPC), comprising groups of physicians in disciplines that use biologics, suggests switching studies with well-defined standards and a minimum of three switches between the products in question, not the two switches currently included in the draft guidance. It also reiterates the importance of caution in extrapolating data between indications and clear information on the extent of interchangeability of a product for the various potential indications.[21] A representative from the American College of Rheumatology (ACR) also noted that appropriate information for safe use must be readily available in the packaging of biosimilars.[22]

Conclusion

Scientific, legal, and regulatory issues will be important for ensuring safe and effective use of biosimilar drugs now and in the future. Aspects of this process may be unfamiliar, and well-informed pharmacists will be an asset to the healthcare team as more biosimilars are developed and marketed. Part 2 of this two-part article will cover the current biosimilars market in the United States and issues related to their use in clinical practice.

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