Is a Biologic Produced 15 Years Ago a Biosimilar of Itself Today?

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Much of the testing required for the regulatory approval of a biosimilar is focused on proving that the new drug is sufficiently similar to the reference biologic in structure, pharmacokinetics or pharmacodynamics, clinical efficacy, and safety. However, the reference drug may itself have gone through some changes in the years since its approval, including those caused by alterations in the manufacturing process. Do these changes increase the risk that the reference drug may cause unexpected outcomes? It is up to the US Food and Drug Administration to decide whether the changes merit the need for additional studies to confirm that the drug meets the structural or clinical outcomes standard for the reference agent. Although it is extremely rare, a change in the production of one biologic drug (ie, epoetin alfa) did result in unanticipated serious immunologic side effects.

KEY WORDS: biosimilarity, biosimilars, darbepoetin, epoetin alfa, etanercept, manufacturing changes, reference drug

The goal of biosimilar manufacturers is to create a drug that features a chemical structure that is extremely close to or the same as the reference or originator drug, demonstrating sufficiently similar morphology and clinical efficacy and safety outcomes that are essentially the same as the reference drug.

The US Food and Drug Administration (FDA)’s pathway to biosimilar approval requires the manufacturer to conduct pharmacokinetic and pharmacodynamic studies that establish equivalent absorption, half-life, binding, and other important parameters. The clinical studies must not reflect any significant differences in outcomes from the reference drug, and, in particular, from the US-licensed version of it.1,2

In the evaluation of Sandoz’s application for an etanercept biosimilar this past July by the FDA Arthritis Advisory Committee, the manufacturer had to go a step beyond proving equivalence to 1 reference drug. Because its clinical studies compared this agent with the European Union (EU)-licensed version of Amgen’s etanercept (Enbrel), Sandoz was also required to prove that the EU-marketed Enbrel was essentially the same as the US-licensed version of the drug (“bridging” studies).2,3 This implies that Enbrel sold in the United States and in the European Union may somehow not be the same, which is exactly the point.

There is a level of uncertainty about the equivalence—and the “practical interchangeability”—of these reference molecules from the same manufacturer.

It may well be that this level of uncertainty is acceptable to the FDA, but this situation is not generally understood by clinicians, policymakers, and the public, who may view biosimilars cautiously for analogous reasons. In this article, we explore why these variations may exist, and why the reference biologic may over time be a biosimilar of the drug that was originally approved by the FDA.

This discussion applies to etanercept, as well as to virtually any biologic that has been produced for many years. Etanercept was introduced in the United States in 1998. The FDA approval of Sandoz’s etanercept-szsb (Erelzi) on August 30, 2016, could make this agent available to patients in 2017, pending the resolution of any remaining patent issues. During nearly 20 years of production of etanercept by Amgen, changes in several areas could potentially alter its intended clinical effects.

Structural Complexity Breeds Uncertainty

Biologics are extremely complex molecules, and this complexity begins with their synthesis. The cell lines that are used to produce the molecules are very specific. Several cells have been used to create biologic drugs, including bacterial, yeast, plant, and mammalian. Manufacturers prefer cell lines that closely mimic human cells for the production of biosimilars (eg, Chinese hamster ovariess and murine lymphoid cells).4

Patents issued for biologic agents describe to some extent the manufacturing process for particular drugs, which is proprietary and highly protected. Biosimilar drug makers are therefore often forced to “reverse engineer” the molecule; that is, start with the final drug and work their way backwards in an effort to develop a new
method of producing the same amino acid sequence, structure, and folding properties of the reference drug.

However, it may not be possible (or practical) to re-create the active ingredient without the addition of side chains or glycosylated groups, which may change the clinical or immunogenic properties of the new molecule compared with the innovator molecule.

Developing a biosimilar drug is challenging, because any slight changes in the structure of the drug (eg, changes in the protein by altering the amino acid sequencing as well as the protein folding) have the potential to modify the efficacy, safety, and quality of the drug in development. In addition, any changes in the structure may also affect the metabolism, formulation, or stability of the biosimilar. There are also challenges to manufacturing the biosimilar. This includes alterations in the fermentation temperature, pH level, filtration, and purification of the reference drug. Even the inactive components of the biosimilar (eg, stabilizers, solubilizers, buffers, pH, bulking agents) may affect aspects of the reference drug, particularly by influencing its immunogenicity.

Even without changes to the reference drug by the manufacturer, slight modifications in the molecule’s construction may occur as a result of changes in the production site, or in the method of production (eg, new technologies used in an effort to increase production). Changing production sites may mean slightly different humidity levels, for example. Manufacturing a new cell line to develop biosimilars adds additional complexities to these complexities.

The FDA is responsible for monitoring these types of alterations in reference drugs, and checking the nature of the newly produced biologic compared with the existing reference drug.

**What Is a Significant Change?**

At what point do changes in the aspects of the manufacturing process render a reference drug a biosimilar of itself? If we consider the FDA’s definition of a biosimilar, the biosimilar must demonstrate only “minor differences in clinically inactive components” compared with the reference agent.

The FDA’s monitoring efforts and regulations deem that certain manufacturing processes do not result in different efficacy or outcomes, and do not mean that the drug has now been transmuted into a biosimilar; however, this is not so cut and dried.

Arguments for both sides have been published, first by McCamish and Woollett, who stated that reference drug manufacturers are essentially creating biosimilars today. Declerck and colleagues claimed that molecules that undergo manufacturer changes are technically and functionally not biosimilars of the original drug.

Depending on what the change is, and the perceived level of risk associated with that alteration, the FDA may decide not to intervene. If the manufacturer believes that a modification in production site may mean a high risk for changed morphology or protein folding, the FDA will consult with the company and approve or disapprove the change plan. In cases of minor process adjustments, the drug maker may make the alteration before notifying regulatory agencies of that change.

**Common Process Changes**

These types of changes are hardly rare. After a drug’s approval, changes in the manufacturing of anti-tumor necrosis factor biologics have occurred with regularity. Through 2012, for example, AbbVie has changed processes associated with adalimumab (Humira) 18 times, and infliximab (Remicade) had 36 changes (Table). Other drugs that have not been on the market for quite as long have had fewer reported changes in manufacturing.

Biologics that undergo manufacturing changes over time may have been considered to be different to some extent. Therefore, the compounds are not necessarily identical any longer to the original drugs, before and after the change. Regulators must deem that the manufacturing changes did not produce any unpredicted or further adverse effects on the drug’s safety or efficacy. The regulator will need to evaluate new comparability studies after such process changes are made. These may not require additional clinical studies, but are likely to involve recharacterization of the molecule. Regulators tend to rely on surveillance efforts to identify important clinical or safety signals.

Transparency in changes within the drug production process is a challenge in the United States. Data on process change and comparability to the originator drug are not in the public domain. However, similar information regarding drugs sold in the European Union is periodically available.

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**Table**

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<th>Drug</th>
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<td>Infliximab (Remicade)</td>
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<tr>
<td>Etanercept (Enbrel)</td>
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<tr>
<td>Adalimumab (Humira)</td>
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<tr>
<td>Abatacept ( Orencia)</td>
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<td>Golimumab (Simponi)</td>
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FDA indicates US Food and Drug Administration.

Biologic agents are entering a new phase of competition as biosimilars begin to enter the marketplace. Increasing numbers of competitors should theoretically lead to more price competition, with manufacturers seeking ways to more efficiently produce their medicines.

A Cautionary Tale

Before the biosimilar approval pathway was implemented, concerns over the implications of biologic manufacturing process changes had long existed, but were little considered outside of drug regulators. As long as the FDA monitored process changes and raised no red flags, payers, providers, and patients did not express concern until a problem arose.

Such a problem, although extremely rare, did occur, and was first recognized in France.12,13 A version of epoetin alfa, sold as Eprex by Johnson & Johnson in Europe, had been produced since 1988. In 1998, the manufacturer introduced a new subcutaneous injection form of epoetin for use in patients undergoing hemodialysis for chronic kidney disease. To allow the change in route of administration, the biosimilar was re-launched in France for the new route of administration in 2008.

One example is darbepoetin alfa (Aranesp), which underwent 18 process changes during its time on the market in the European Union. A manufacturing change in 2008 involved the drug’s recombinant DNA sequence.10 The European Medicines Agency (EMA) mandated that the drug maker conduct clinical studies to prove that the latest version of the biologic was comparable to the previous compound. In this case, the EMA agreed that this 2008 version of Aranesp was not clinically different from the reference drug.10

Biologic agents are entering a new phase of competition as biosimilars begin to enter the marketplace. Increasing numbers of competitors should theoretically lead to more price competition, with manufacturers seeking ways to more efficiently produce their medicines. According to Pierre Michetti, MD, Crohn and Colitis Centre, Gastro-entérologie La Source-Beaulieu, Lausanne, Switzerland, “This price pressure will push the biological drug producers to seek for savings along the drug production chain and the product testing process. This pressure will translate itself into an increased number of manufacturing changes, a number which will grow with the number of players and with the market expansion that lower prices will certainly also induce.”11

Interview with Aimee K. Tharaldson, PharmD, Express Scripts

We conducted a brief interview on biosimilars with Aimee K. Tharaldson, PharmD, Senior Clinical Consultant, Emerging Therapeutics, Express Scripts, a company that provides pharmacy benefits management and specialty pharmacy services, on several biosimilar-related issues.

Q: Are you concerned that a biologic, such as Enbrel, may not be the exact same molecule produced today as in 1998?

Dr Tharaldson: Changes in the exact cellular makeup of biologic drugs frequently occur when a company changes its manufacturing process to improve efficiency, increase batch size, or move to another site, for example. Even with none of these moves, there is a level of inherent variability in making biologics. Regulators, so far, have been satisfied that manufacturing-driven changes in a biologic medication have not altered its safety or efficacy, and have allowed the medication to continue to be sold under the existing name and label, and that has been happening for years. It is yet another reason why there should be a clearer pathway, greater interchangeability, and more widespread use of biosimilars in the United States.

Q: Do you think an interchangeable designation will matter in the long-run, or will biosimilar drugs be switched anyway?

Dr Tharaldson: We believe in removing any roadblocks that prevent the adoption of biosimilars. The lack of an interchangeable designation makes the prescribing of biosimilars more confusing and complex, ultimately leading to fewer patients using a biosimilar drug.

Q: What kind of conversations have you had with your payer clients regarding the biosimilar pipeline?

Dr Tharaldson: For several years, Express Scripts has advocated strongly for biosimilars in the US market, and we have been working with our clients to help them understand the potential savings that can be achieved when biosimilar competition enters the market. We keep them informed on the pipeline and when we can expect some of these drugs to become available on the market.
tion, the drug maker used polysorbate 80 and glycine, replacing human serum albumin, as a stabilizer.12,13

The first safety signal was loud: within a few months of use, 12 French patients were identified as having antibodies to epoetin, causing pure red-cell aplasia.13 Multiple cases were found throughout Europe, and pure red-cell aplasia was demonstrated in 191 patients, of whom 95% had received the new subcutaneous form of the drug.13

Biologic agents that undergo several process changes may be more likely to be different from when they were originally tested, approved, and produced more than a decade ago.

Conclusion

New biosimilar manufacturers must prove that their drugs are equivalent in terms of their structure, pharmacokinetics, pharmacologic and clinical effects, safety profile, and tolerability. In the case of a biosimilar manufacturer that requests and receives a sample of the reference drug, several years may be required to conduct the necessary studies and evaluations to engineer the creation of a biosimilar to this agent. If the reference drug has had 1 or 2 process changes during that time, is the investigational biosimilar now viewed with the latest reference drug or the original version?

If we consider the 30,000-foot view, is not a biosimilar, from the FDA’s perspective, the result of a manufacturing process change from the innovator biologic? The FDA requires comparability studies for the new process of creating a very close reproduction of the original molecule. Granted, the process changes associated with biosimilars are radical, but the comparison does ring true.

Biologic agents that undergo several process changes may be more likely to be different from when they were originally tested, approved, and produced more than a decade ago. It is on this basis that one might consider today’s long-available biologics, in some cases, as biosimilars to themselves. However, even if this is the case, reports of altered clinical or safety profiles of such compounds have been exceedingly rare.

Author Disclosure Statement

Mr Mehr has provided consulting to Boehringer Ingelheim.
Ms Zimmerman reported no conflicts of interest.

References