Implications of the FDA Draft Guidance on Biosimilars for Clinicians: What We Know and Don’t Know

Edward Li, PharmD, BCOP, and James M. Hoffman, PharmD, MS, BCPS

The Patient Protection and Affordable Care Act of 2010 included the Biologics Price Competition and Innovation Act (BPCI Act), which enables the introduction of biosimilar agents to the US market. Generally, biosimilar agents are copies of therapeutic proteins that are not manufactured by the innovator (ie, the reference product) and are approved under an abbreviated regulatory process. More specifically, the BPCI Act defines biosimilars as biological products that are “highly similar” to the reference product, notwithstanding minor differences in clinically inactive components. Thus, there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. Europe has led the way in developing regulations for biosimilars, and a European working group has proposed more precise terms for biosimilars and related concepts.

Interest in biosimilars has been driven largely by economics—because most biologic agents are expensive therapies—and the introduction of biosimilars presents new cost-saving opportunities. The NCCN completed a comprehensive evaluation of the implications of biosimilars on cancer care and published a white paper. The NCCN white paper outlines how biologic agents and biosimilars differ from small-molecule or chemical medications and describes how these differences have driven the development of a new regulatory pathway.

The paper also notes that biologics are widely used in cancer care; therefore, oncology clinicians have a great interest using biosimilars in the future. Ultimately, the acceptance and uptake of biosimilars in routine clinical practice will be determined by the comfort level of practitioners and payers when reviewing the evidence of biosimilarity and clinical data.

The BPCI Act outlined broad concepts for the approval of biosimilars in the United States, and experts recognize that more specific details on the requirements for the biosimilar approval process are needed. Since the passage of the law, many people, including health care practitioners, manufacturers, and patients, have looked for guidance from the FDA to further define pathways to allow for the introduction of biosimilars into the US market. In February 2012, the FDA released the first biosimilar guidance for comment. This represents an important next step in defining the approval pathway. The draft biosimilar guidance presents some progress toward resolving relevant clinical issues, but some questions remain unanswered. In this commentary, we present a brief review of the FDA draft guidance, and discuss 2 important topics as identified by the NCCN Biosimilars Work Group: 1) generic substitution and interchangeability and 2) extrapolation of biosimilarity data to other FDA-approved and off-label indications.

Draft Guidance

The draft guidance documents address how the FDA plans to implement a biosimilars pathway, as well as quality and scientific considerations when developing a biosimilar product. Although these documents are primarily addressed to industry stakeholders (ie, those interested in developing a biosimilar product or those currently with a marketed
Commentary

Biosimilars

James M. Hoffman, PharmD, MS, BCPS

James M. Hoffman, PharmD, MS, BCPS, is Associate Member in the Pharmaceutical Sciences and Medication Outcomes and Safety Officer at St. Jude Children’s Research Hospital, and Associate Professor of Clinical Pharmacy in the College of Pharmacy at the University of Tennessee Health Science Center.

Dr. Hoffman’s contributions to this paper were supported by the Cancer Center Core Grant #NIH CA 21765 and the American Lebanese Syrian Associated Charities (ALSAC).

biologic product), practicing clinicians may still find this information useful. These documents provide the underlying principles of what data the FDA will require from manufacturers to establish biosimilarity (and subsequently interchangeability). By understanding these principles, clinicians will be well positioned to review biosimilar products and assess whether they should be used in their patient populations. That these guidance documents are in draft form is important to note; a public hearing was held in May 2012 to collect public feedback (with comments accepted through May 25, 2012).\(^5\)

The first document, *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*, sets forth the principles of how analytical studies should be used when assessing the physiochemical and functional properties that factor into a determination about whether a product is biosimilar to the reference product. Accordingly, factors regarding expression systems, the manufacturing process, assessment of physiochemical properties, functional activities, receptor binding, product impurities, and stability are discussed.\(^6\) Although this type of information is important for determining biosimilarity to the reference, interest to practicing clinicians is likely to be low.

Clinicians will likely find more value in the second document, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, because it discusses what types of evidence will be reviewed to determine whether a biologic product is biosimilar to a reference product. As proposed by the FDA, data packets supporting the demonstration of biosimilarity will contain a structural and functional analysis comparing the biosimilar to the reference product. Additionally, in vivo animal data comparing toxicity and pharmacokinetic and pharmacodynamic parameters may be included. Immunogenicity studies in animals may be used as well.\(^7\) Further, the FDA guidance clarifies that a proposed biosimilar product “must include” data showing that “there are no clinically meaningful differences between the [biosimilar] product and the reference product in terms of safety, purity, and potency.” Thus, human clinical studies will be required as part of the data packet submitted to the FDA for consideration to approve a potential biosimilar. This means that data informing pharmacokinetic/pharmacodynamic, clinical immunogenicity, and clinical safety/efficacy will be required. Postmarketing data for safety concerns may be required as well. The FDA notes that the amount of preclinical and clinical data that will be required in an application will depend on the specific product being reviewed; no standard threshold has been established for the scope and magnitude of data required for the FDA to approve a biosimilar product. Instead, the FDA emphasizes that they will use a “totality of the evidence” approach when considering a proposed biosimilar product. Taking these factors into consideration, the labeling of the biosimilar product will explicitly state whether it is biosimilar to a reference for specific indications and whether it is deemed to be interchangeable to the reference.\(^7\)

Although these documents are helpful, they do not present a complete picture of this complex issue, and some questions remain. We believe that the FDA’s “totality of the evidence” approach is appropriate, but it does not provide specific details regarding what clinical studies will be required of each proposed product. As the FDA works to streamline the regulatory approach to biosimilars, the regulatory guidelines used in Europe (where class-specific biosimilars guidance is provided) could be used as a model.\(^8,9\) If and when these class-specific guidelines are developed in the United States, the process should be transparent. An open dialogue among all stakeholders will be essential for the successful implementation of these regulations.
Biosimilar Substitution and Interchangeability

When the FDA approves a small-molecule generic drug, it does so under the Drug Price Competition and Patent Term Restoration Act of 1984 (often referred to as the Hatch-Waxman Act). Such an approval allows the generic drug to be marketed after demonstration of bioequivalence data, and this information is readily available in an FDA publication, Approved Drug Products With Therapeutic Equivalence Evaluations (also known as The Orange Book). Based on bioequivalence information published within The Orange Book, individual state laws may allow pharmacists to independently and automatically substitute a branded small-molecule drug with the generic version without prior approval from the prescriber. In some states, patient consent or notification is not explicitly required.

It is important to note that the current practice of automatic substitution does not legally transfer to biosimilar products. Most state laws explicitly mention using the criteria listed in The Orange Book as the basis for automatic substitution, but the publication does not address biologic products. Thus, under current law in most states, automatically substituting a biosimilar for the reference product may be interpreted as being beyond the pharmacist’s scope of practice.

Although the FDA guidance affirms that biosimilarity and interchangeability information will be provided in the biosimilar product’s labeling, individual state laws will likely require an explicit statement about whether automatic substitution of biological products can or cannot occur without consulting or notifying the prescriber or patient. Importantly, the concerns about automatic substitution mostly apply to patient care that occurs in the community pharmacy practice or specialty distribution (eg, mail order) setting; hospitals, health systems, or community-based oncology practices may adopt their own, locally approved substitution practices based on a formalized process.

Recently, legislation was introduced in several states to address pharmacist-initiated automatic substitution of a biosimilar for the reference product. Although some details of the proposed legislation are different in each state, there are similar themes and elements in each of these proposals. The proposed legislation would allow pharmacists to automatically substitute FDA-designated interchangeable biosimilars for their respective reference products with the following conditions: 1) the pharmacist must notify the prescriber and patient (or patient’s representative) regarding the substitution; 2) the physician has the ability to request that the biologic be “dispensed as written” (ie, explicitly request that the biologic not be substituted); and 3) any substitution must be documented and records must be maintained. Critics of these proposals argue that they are overly restrictive and potentially conflict with federal law because interchangeable biosimilars are defined in the BPCI Act as those that can be substituted by a health care practitioner without consulting the prescribing physician. Supporters of the state proposals cite the complexity of these molecules and suggest that these laws are needed to support patient safety. For clinicians, following and becoming engaged in future debates and discussions about biosimilar substitution in individual states will be important, because these regulations will ultimately affect the process of care delivery on a day-to-day basis.

Extrapolation of Biosimilarity Data to Other FDA-Approved and Off-Label Indications

When a biosimilar product is approved by the FDA, the product’s labeling on whether the product is deemed to be biosimilar or interchangeable to (and interchangeable with) the reference product includes FDA-approved indications only. However, a situation may arise in which a product has only been deemed as biosimilar or
interchangeable to one of many FDA-approved indications. This raises questions about whether the sponsor of the biosimilar product will conduct further studies in the other indications. Certainly, this depends on whether there is sufficient incentive to obtain the data—thus, indications for less common diseases may not be of priority—and whether the FDA can or will mandate that biosimilarity trials for those particular indications be conducted.

Anticancer biologic therapies are also commonly (and appropriately) used for indications beyond the FDA-approved labeling. Obtaining biosimilarity information for these indications presents challenges because such assessments cannot and will not be addressed by the FDA. Off-label indications are beyond the control of the FDA; thus a mandate to conduct these studies is not realistic. Therefore, biosimilarity studies for off-label indications will likely be conducted outside of a formal FDA approval process and will likely need private or public grants for funding. However, biosimilar studies may not be a high priority for cooperative groups or the granting agencies.

In situations with an absence of biosimilarity data for a particular indication, clinicians must make a determination about whether to use the biosimilar product for the off-label indication. This highlights the need for expert judgment, based on a thorough review and an extrapolation of the available data in other indications. Accordingly, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) could provide explicit language regarding whether the extrapolation of biosimilarity to indications that have not been studied is appropriate or inappropriate (based on the expert judgment of the panel members).

Future Implications

The release of the draft guidance documents on biosimilars represents an important step toward obtaining approval of these products in the United States. Although the documents are more useful to manufacturers who are developing (or considering developing) a biosimilar product, these documents also provide useful information for clinicians about the type of evidence that the FDA will require to determine biosimilarity. Because many aspects of the clinical use of biosimilars were outside the scope of these documents, however, clinicians will need to also stay informed on biosimilar developments, including the release of new evidence establishing biosimilarity of specific products.

The NCCN Biosimilars Working Group has recommended that the NCCN Guidelines address biosimilars on a case-by-case basis. Accordingly, the NCCN Guidelines should provide insight as to whether extrapolating use of a biosimilar to other unstudied indications is accepted. If extrapolation is judged to be acceptable in certain indications, follow-up surveillance studies to confirm biosimilarity should be considered. The use of secondary data will likely play a large role in this regard, and the need to identify the specific source of the product is paramount.

Understanding the developing issues surrounding biosimilars will position individual clinicians and organizations to make better decisions on the best use of biosimilar products for their patients. Institutions should use formalized processes to evaluate individual biosimilar products and draft policies guiding their use within their patient population. For example, the formulary process and approval through the Pharmacy and Therapeutics Committee within hospitals and health systems could be one such mechanism of review and oversight. The FDA appears committed to safely implementing and monitoring the use of biosimilars, and clinicians should monitor developments at the state level regarding automatic substitutions of these products.
References