

Jessica K. DeMartino, PhD

Jessica K. DeMartino, PhD, is Manager of Health Policy Programs at NCCN. The health policy focus at NCCN has recently included comparative effectiveness research (CER) and risk evaluation and mitigation strategies (REMS). Dr. DeMartino earned her Bachelor of Science degree in biochemistry from the University of Delaware and her PhD in organic chemistry from The Scripps Research Institute.

Biosimilars: Approval and Acceptance?

On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act. The Affordable Care Act contains a subtitle “Biologics Price Competition and Innovation Act of 2009” (BPCI Act) with information that establishes an abbreviated approval pathway for biologic products that are shown to be “highly similar” to or “interchangeable” with an FDA-licensed biological product.

A biologic agent is a product derived from living sources, such as viruses, bacteria, or human and other animal sources. General classes of biologic agents include monoclonal antibodies, complex sugars, blood derivatives, vaccines, and recombinant or purified proteins such as cytokines, thrombolytic agents, and enzymes. The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the *Hatch-Waxman Act*), which established abbreviated pathways for the approval of drug products (i.e., “generics”) under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The BPCI Act aligns with the FDA’s longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing. However, biologic agents can present challenges to implementing an abbreviated approval pathway for many reasons. First, biologics are considerably more complex than most chemical entities due to increased molecular weight, complicated and patented manufacturing processes, immunogenicity issues, and analytical issues related to determining properties unique to these agents. Second, the clinical consequences of subtle differences in biosimilar products may vary; therefore, assessment on an individual product basis is warranted.

Establishing Biosimilarity

Section 351(k) of the Public Health Service Act, as modified by BPCI, describes general requirements for establishing biosimilarity. A biologic agent may show biosimilarity to a reference product based on data derived from analytical studies, animal studies, and clinical studies. To determine and assess biosimilarity, analytical techniques must be able to examine primary sequences, secondary and tertiary structures, folding, post-translational modifications, and aggregation. However, the ability to determine structural differences is not enough. Whether the structural differences have an effect on clinical activity is the real question. Although Section 351(k) does not specify what type of clinical studies will be needed to show biosimilarity, an assessment of immunogenicity and pharmacokinetics or pharmacodynamics studies will most likely be required.

The BPCI Act gives the FDA discretion to determine what studies are needed to establish biosimilarity for any given product. Although discretion may allow for the quickest approval of biosimilar agents, this process means that every biosimilar manufacturer must discuss what is necessary to establish biosimilarity with the FDA. One possible solution

is the development of class-wide guidance, with the option to approach the FDA for a waiver to the guidance.

Many biologic agents have multiple FDA-approved indications and established “off-label” uses. Whether the manufacturers of biosimilar agents will or should be responsible for establishing biosimilarity for all FDA-approved indications is not clear. Applying biosimilarity to all indications will be difficult and should depend on individual circumstances and properties. For example, is the mechanism of action the same in all indications? Are immunogenicity issues expected?

Off-Label Uses

Concern may be even broader for off-label uses. Because of current FDA regulations, manufacturers cannot address off-label indications, but this issue will be of major concern in oncology. Some physicians may be unlikely to prescribe a biosimilar drug for an off-label indication for a life-threatening disease without evidence or data to support its use. Even if a drug is already known to be safe and effective in one indication, physicians may be unwilling to prescribe a biosimilar that has not also been proven safe and effective in that particular off-label indication. Pharmacists may also be uncomfortable with substituting a drug for a different indication than was used to gain FDA approval.

Establishing Interchangeability

Beyond establishing biosimilarity, manufacturers will be working to establish the higher standard of interchangeability. For a biosimilar to be deemed interchangeable, the product must be expected to produce the same clinical results as the reference product in any given patient. For a biologic agent that is administered more than once, the risks in terms of safety and diminished efficacy of alternating or switching between the reference product and the biosimilar must be equal to or less than the risk of using only the reference product. The BPCI Act also establishes that interchangeable products may be substituted for a reference product by a pharmacist without the intervention of the prescribing health care provider.

Currently, what studies are needed to establish interchangeability are under discussion. Each clinical situation may require different switching or alternating studies depending on the mechanism of action, anticipated immunogenicity issues, and clinical setting in which the biologic agent is used. Again, the issue of establishing interchangeability in all FDA-approved indications and all accepted off-label indications is in force. Additionally, how many indications require switching or alternating studies to extrapolate interchangeability to all indications has not been established yet.

Does Interchangeability Equal Automatic Substitution?

Despite the ability to substitute biosimilars that have been deemed interchangeable, many pharmacists and Pharmacy and Therapeutics (P&T) Committees may not be comfortable with automatic substitution for these

DeMartino

biosimilars. Pharmacists and P&T Committees may perform their own analysis on the studies that have been used to establish biosimilarity and interchangeability to determine automatic substitution policies (considering both safety and cost). As a result, clinical parameters as to when substitution is allowed in specific formularies could be much stricter or more liberal than the FDA labeling. Institutions will need to ensure that their P&T Committee includes members with the appropriate expertise to address these issues.

Establishing equivalence sufficient for substitution ultimately depends on the “strength of evidence,” and with biologics, evidence might be presented in a different form than clinicians are familiar with. A better understanding of the required information and how it supports equivalence must be determined by both practitioners and payors.

Ultimately, physicians and other practitioners will control the uptake and incorporation of biosimilars into clinical practice. Oncologists and other practitioners will need to be aware of the science behind biosimilarity and interchangeability. Because of the clinical seriousness of treating patients with cancer, clinicians likely will need great confidence in the data supporting biosimilar approval and associated safety to use a biosimilar product over an innovator biologic agent.

Additionally, the widespread acceptance of off-label uses of biologics in oncology means that practitioners will probably also need to extrapolate data for FDA-approved indications to accepted off-label uses. Equivalent dosing must also be established, and whether the drugs will be provided in “metric” or “active unit” doses must be determined. Considering the size of the molecules and the potential molecular variance of the inactive part of the molecule, new potency standards may be required.

Biosimilars in Everyday Practice

The day-to-day care of patients with cancer also requires a fine balance in naming conventions, which must effectively relay information about the differences between the innovator and biosimilar products while maintaining a sense of interchangeability (if the biosimilar product is deemed interchangeable). In the interest of patient safety, patients, clinicians, and pharmacists must be able to easily differentiate between innovator and biosimilar products. Clinicians and pharmacists must also be able to easily distinguish which medications are interchangeable to make medical decisions. Naming and labeling biosimilars will greatly affect the ability of clinicians to safely prescribe and dispense medications. The use of unique nonproprietary names has been raised as a possible naming solution, but some experts believe that the innovator and all biosimilars should have the same generic name.

One example solution already in place is the generic naming of botulinum toxin—onobotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA, and rimabotulinumtoxinB—incorporating different prefixes. This type of system distinguishes the drugs, while retaining an element of commonality in all the names. The quandary comes in determining which option is best and allows for the safest treatment. Using different names may allow for straightforward pharmacovigilance, making it easier to track and report

Biosimilars

adverse events and immunogenicity reactions of specific biosimilar products.

In conclusion, the use of biologics is widespread in the active treatment of cancer and for supportive care. As the use of biologics continues to grow and patents expire for older biologic agents, consideration is needed for incorporating biosimilars into clinical practice while maintaining safety and improving outcomes for patients with cancer. Oncologists and pharmacists must be aware of the scientific issues surrounding biosimilars and must equip themselves with the knowledge and skills required to effectively assess the data supporting biosimilars to determine the safe and effective use in patients with cancer.