

Determining Bioequivalency in Similar Biopharmaceuticals Neuromuscular

Richard Wenzel, PharmD

For a CME/CEU version of this article please go to <http://www.namcp.org/cmeonline.htm>, and then click the activity title.

Summary

The availability of pharmaceutical agents derived from biologic sources continues to expand. As the patents on these biologic agents expire, the issue of generic or biosimilar agents has become a problem. There currently is no good method to determine bioequivalence and thus substitutability between two biosimilars. Comparing labeling information is one method that may be helpful in the interim.

Key Points

- A way to determine bioequivalence for biosimilar biologic products is needed.
- The FDA will likely use European Union methods as a model to develop guidelines for this country.
- Until a better method is available, using the labeling information is one relatively quick, economical way to compare biopharmaceuticals.

ISSUES RELATED TO THE PRESCRIBING brand-name medications versus generic medications were common approximately 20 to 25 years ago. Today, generic medications are widely prescribed, well accepted by the public as safe and effective, generally viewed as a clinical and economic success, and almost universally preferred by managed care organizations. The majority of the current generic medications are molecularly small, easily chemically synthesized compounds, oral formulations, and pharmacologically targeting one receptor or body site. A few examples are famotidine, simvastatin, and propranolol.

One of the things that really enabled the success of the generic medications was the Drug Price Competition and Patent Term Restoration Act of 1984, better known as the Hatch-Waxman Act. This created an abbreviated approval process for generics. It required generic manufacturers to demonstrate bioequivalence to brand-name products, but allows manufacturers to rely on the brand-name medication's clinical trials to establish safety and efficacy. This act allows generic testing before the brand name's patent expires and created incentives for generics to challenge brand-name patents. Additionally, the act established a process to address patent disputes and extensions. FDA bioequivalence standards require the same chemical composition as determined by nuclear magnetic resonance or mass spectroscopy between the generic and brand name products.¹ Similar bioavailability is determined by pharmacokinetic rate and

extent of absorption studies. This is easily done with simple, chemically synthesized compounds.

The world of generics is changing with the introduction of a large number of biopharmaceutical agents. Biopharmaceuticals or biologics are medicinal agents produced by and purified from a biological (living) source.² The majority of biopharmaceuticals are proteins derived via recombinant DNA technology applied to genetically engineered bacteria. These agents are typically administered via injection and are large, heterogeneous molecules. Exhibit 1 compares ranitidine and epoetin, a typical biopharmaceutical.

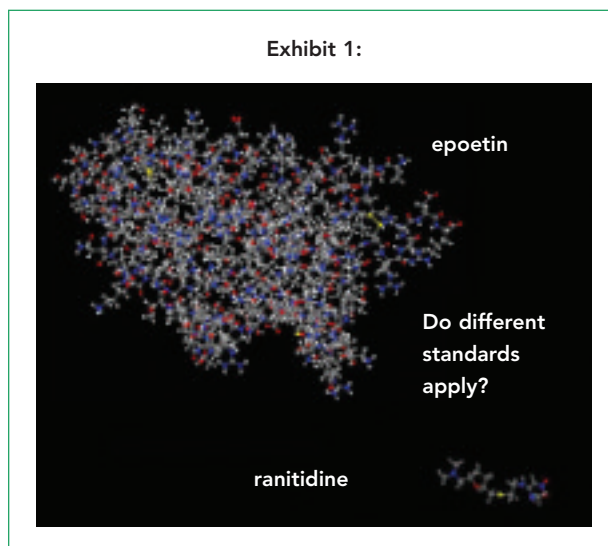
Biopharmaceuticals are definitely the future of drug therapy. In 2006, 418 biopharmaceutical products were in various stages of development.³ It is estimated by 2010, that 50 percent of newly approved FDA products are going to be biopharmaceuticals. Fewer traditional medications (i.e., small, chemically synthesized compounds) will be brought to market. In 2006, total sales of biopharmaceutics in the United States was \$40 billion.² That figure is only going to increase exponentially. Biopharmaceutics are probably already a large portion of most managed care plan expenditures and, in the future, are likely to be the number one medication expenditure in most budgets.

Numerous biopharmaceutical compounds were FDA approved in the late 1980s and early 1990s. Exhibit 2 shows some of the best selling products approved before 1993.⁴ The majority of the early approved agents are now nearing their patent expiration.

Historically, patent expiration offers opportunities for generic manufacturers. Currently, few generic biopharmaceuticals are in development due to unique barriers.¹ There are not a lot of companies lined up and ready to start making biopharmaceuticals, and that is a problem because generics produce price competition.

One major issue is what to name copies of biologics. “Generic biological” is considered an inappropriate term because this implies an exact copy of the original product, with the exact pharmaceutical actions. This is currently impossible to demonstrate due to technology limitations. “Follow-on biological” (FOB) is the most common term used in the literature. The FDA frequently uses follow-on biological. Biosimilar also appears in some publications and is the term, which will be used for this article.

Noting the differences between traditional medication and biopharmaceuticals, one can recognize that there will be some issues demonstrating bioequivalence between an original or brand name biopharmaceutical and a generic compound. There



are quite a few unique barriers to the development of biosimilars. Exhibit 3 lists the major barriers to determining equivalency with biosimilars.

Exhibit 2: Top-Selling Biopharmaceuticals Approved before 1993.*

Drug	Indication	Approval Date	2003 Sales \$ (millions)
Humulin (human insulin)	Diabetes	October 1982	1,060
Intron A (interferon alfa-2b)	Cancer, infection	June 1986	1,851
Humatrope (somatropin)	Growth failure	March 1987	371
Infanrix (diphtheria-tetanus-pertussis vaccine)	Immunization against diphtheria, pertussis, and tetanus	March 1987	551
Epogen (epoetin alfa)	Anemia	June 1989	2,435
Engerix-B (hepatitis B vaccine)	Immunization against hepatitis B	August 1989	684
Botox (botulinum toxin type A)	Cervical dystonia	December 1989	564
Epogin (epoetin beta)	Anemia	April 1990	551
Procrit (epoetin alfa)	Anemia	December 1990	3,984
Neupogen (filgrastim)	Neutropenia	January 1991	1,267
Cerezyme (imiglucerase)	Gaucher's disease	April 1991	739
NovoSeven (recombinant factor VII)	Hemophilia	April 1992	589

Reference: 4

Exhibit 3: Barriers to Demonstrating Equivalency of Biosimilars

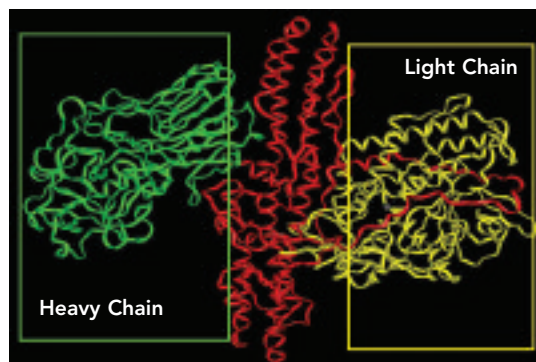
- Molecularly large, heterogeneous protein structure
- Complex modes of action, targeting multiple receptors and other sites within the body
- Traditional assays (e.g., magnetic resonance spectroscopy) are difficult to perform and may yield ambiguous results.
- Other technological limitations

One of the interesting things about biopharmaceuticals is that most companies do not patent the compound; they patent the production process.⁵ Production methods often are closely held by the companies as intellectual secrets, which creates another barrier in terms of comparing these products.

For most of these products, the production process is rather lengthy and complex. The physiologic and clinical properties of these biopharmaceuticals can be changed if the production process is changed. Production changes can alter the ratio of impurities, alter the composition of production-related substances, especially the creation of proteins, and, most importantly, can ultimately alter overall clinical effects.

The big question with biosimilars is how does one demonstrate equivalency of versions of original compounds. The answer is unknown at this point. Currently, the United States lacks regulatory guidelines governing either the process or the implementation of criteria for judging the bioequivalence of biosimilars. A process of who and how to determine equivalence to the existing products and, therefore, whether they can be substituted for each other, needs to be developed. A need exists for new, technologically sophisticated and validated methods to uniformly assess biopharmaceuticals. This past summer, the U.S. Senate debated the issue of biosimilars without much consensus.⁶ The two

Exhibit 4: Botulinum Neurotoxin Type A Structure



major issues in this debate were how long original biopharmaceuticals should have market exclusivity and who should determine bioequivalence—the FDA, the physician, or the payer. The European Union (EU) has addressed the biosimilar issue to a greater extent than the FDA.⁷ The FDA will likely use EU methods as a model to develop guidelines for this country.

There are a few key points from the EU guidelines. The company will have to demonstrate or justify that the new and original/reference products have similar profiles in terms of quality, safety, and efficacy.⁷ This is a big difference between how generics come to market where they use the data that already existed from the brand name to demonstrate efficacy and safety. Companies are going to have to spend a lot of time and money because they are basically bringing a new drug to market. The EU guidelines note that data will have to be judged on a case-by-case basis. Because each case is unique, this leads to frustration on the developing companies part. At this time, companies do not know what the FDA will want in each case so they are not sure what type of studies to do.

Exhibit 5: Product Description Physical Characteristics

	Dysport®	Botox®
Strain of <i>C. botulinum</i>	NCTC 2916	Hall
Serotype	A	A
Isolation methods	Acid precipitation, column chromatography	Dialysis, acid precipitation
Complex molecular weight 1< (Da)	500-900	900
Units/package	500	100
Neurotoxin protein content n (g/vial)	12.5	~5
Formulation	Lyophilized	Vacuum dried
pH	~7	~7
Excipients	Human albumin with lactose	Human albumin with 0.9 % NaCl

Reference: 10

Additionally, the FDA does not know what data it wants in a particular case either.

Immunogenicity is a concept that has not been a major issue with traditional medications. There is a high risk of immune-related adverse events with biologics because proteins in these products can be seen as foreign, invading proteins by the body's immune system. The EU guidelines note that immunogenicity must always be addressed by clinical data, unless clinically relevant immunogenicity can be excluded by other means.⁷ The issue of immunogenicity must always be considered when a claim of comparability is made, especially when repeated administration is proposed.⁷ Because repeat administration may not occur for a long time, studies looking at this issue may have to be very long in duration.

Botulinum neurotoxin is one biopharmaceutical that can be used to further examine the issue of biosimilars. This agent was first FDA approved in 1989 and currently has three FDA approved indications.⁸ There also is substantial off-label use for a variety of conditions and considerable ongoing research for additional illnesses.

Botulinum toxin comes from *clostridium botulinum*, which is a gram-positive anaerobe found in the soil and water. *Clostridium botulinum* produces seven serologically distinct potent neurotoxins—A, B, C1, D, E, F, and G.⁹ Toxin A was the first utilized clinically and the most clinical experience exists with this agent. Toxins A and B are commercially available in the United States. All the toxins produce a temporary chemical relaxation of striated muscle and each serotype's molecular structure and intracellular targets are different, which leads to different pharmacologic activity.

All the toxins are large complexes of different proteins (Exhibit 4). One of the key things that must happen once Toxin A is injected, is enzymes within the body “nick” the bonds between some of the proteins. Nicked botulinum toxin is what has pharmacologic activity in the body. This is important because although un-nicked toxin has no pharmacologic activity, it can actually activate the immune system. The different serotypes of toxins differ in the percentage that gets nicked by the body enzymes.

An increasing number of botulinum neurotoxin products (serotypes A and B) are being developed and marketed. Interested parties such as managed care will need to address the relative merits of different products. One economical method is to compare the products based on their Summary of Product Characteristics (SmPC). A study examining the similarities and differences of two botulinum toxin serotype A products, Botox[®] (FDA approved) and Dysport[®] (seeking FDA approval) based upon their worldwide SmPC information was recently published.¹⁰

Exhibit 6: Botox[®] and Dysport[®] Approved Indication

Common approvals

- Blepharospasm
- Hemifacial spasm
- Torticollis cervical dystonia
- Focal spasticity
- Hyperhidrosis
- Spastic cerebral palsy



Botox[®]: all 6 approved
in 18 countries

Dysport[®]: all 6 approved
in 2 countries

Approvals unique to Botox[®]

- Palate myoclonia
- Bruxism
- Bladder hyperactivity
- Anal fissure
- Headache
- Dysphonia
- Tremor
- Pathological contractures
- Achalasia

Reference: 10

Exhibit 5 includes product characteristics and physical descriptions of the two products.¹⁰

The strain of *clostridium botulinum* that these products come from is different, which could lead to a difference in activity, but they are both Serotype A. How they are isolated and the sizes of the molecules are different. There also is a difference in the neurotoxin protein content per 100 units, which may have importance on immune system adverse effects. The majority of SmPCs for both products clearly states that units of biological activity are unique to each botulinum neurotoxin preparation and cannot be compared nor converted into units of another. Units of biological activity are assessed by different means and are thus incomparable.

The worldwide indications for these two products are summarized in Exhibit 6.¹⁰ Exhibit 7 provides dose comparisons for selected indications.¹⁰ As noted in this exhibit, the dose varies for each indication and for each product. Additionally, the doses recommended vary by country. For all indications examined, the dose of Dysport[®] is higher than that for Botox[®]. The recommended treatment duration also varies significantly by indication, country, and product.

Historically, adverse effects have been one way to differentiate between products. Most SmPCs indicated that adverse events with both toxin products are mild to moderate and transient. It is difficult to compare between products, but the majority of the reported adverse effects are very similar (Exhibit 8).¹⁰ Dysphagia was reported in the SmPCs significantly more often with Dysport[®] (26 to 39 percent) versus Botox[®] (12 to 13 percent). Because of the shape and size of the molecule, the higher Dysport[®] rates may be related to a greater tendency of this product to migrate away from the injection site into neighboring tissues. Dysphagia can lead to serious complications such as aspiration of

Exhibit 7: Dose Comparisons

	Dysport®	Botox®
Blepharospasm	120 U/eye; reduce to 60-80 U as needed	12.5-20 U/eye; 100 U max
Cervicaldystonia	500U, 250-1000U; 1000 U max	Individual dosing; 200 U max
Spasticity ²	Arm: 75-1000 U, Leg: 15003U	Individual dosing; 360 U max
Hyperhidrosis ²	Doses not listed	50 U/axilla
Cerebral palsy ²	20-30 U/kg initial, 1000 U max	4 U/kg, 200 U max (Brazil only)

¹Countries included: France, Italy, The Netherlands, Spain, UK, Brazil

²Dysport® not approved for these indications in all 5 countries listed

³Some countries don't specify arm and leg

Reference: 10

food. Some SmPCs suggest limits on sternocleidomastoid injections to avoid this adverse effect. Dysport® is usually limited to less than 150 units for the initial dose and Botox® 100 units. Higher rates of focal pain are reported with Botox®. Injection technique with either product may have an impact on the rate of adverse effects.

Immunogenicity is another area where there may be differences between two biosimilar products. The two botulinum products contain different amounts of neurotoxin protein. Amount of protein is one factor in neutralizing antibody formation. The reported antigenicity rates are approximately 1 to 5 percent across indications for Botox® and 4.7 percent for Dysport.¹⁰ This appears to be very similar for these two products. Because of the comparatively short time periods of most clinical trials with these agents, the complete answer with respect to immunogenicity is not yet known. Continued monitoring of immunogenicity issues within clinical settings will be essential in the future for all biopharmaceuticals.

Ultimately, a favorable immunogenicity profile may distinguish one product from another.

Based on available information from the product labeling, these two botulinum toxin products are different enough to say they are not bioequivalent. There is no universally applicable safe dose conversion. All the package inserts from almost all the countries where these products are approved warn against interchanging botulinum toxin products.

Conclusion

As the patents on biopharmaceutical products expire, biosimilars are becoming an issue. A way to determine bioequivalence for these biologic products is needed. The FDA needs to establish a framework for comparing biosimilars, which will likely be based on the EU guidelines. Until a better method is available, using the information from the labeling is one relatively quick economical way to compare biopharmaceuticals. **JMCM**

Richard Wenzel, Pharm D, is a member of the Diamond Headache Clinic Inpatient Unit at St. Joseph Hospital in Chicago, Ill.

References

- Devine JW, Cline RR, Farley JE Follow-on biologics: competition in the biopharmaceutical marketplace. *J Am Pharm Assoc.* 2006;46:193-204.
- Schellekens H. Follow-on biologics: challenges of the "next generation". *Nephrol Dial Transplant.* 2005;20(suppl 4):iv31-iv36.
- Pharmaceutical Research and Manufacturers of America. 418 biotechnology medicines in testing promise to bolster the arsenal against disease. *Medicines in Development Biotechnology* 2006. Available at <http://www.pharma.org/files/Biotech%202006.pdf>.
- Frank R.G. Regulation of follow-on biologics. *N Engl J Med.* 2007;357:841-843.
- Crommelin DJ, Storm G, Verrijck R, et al. Shifting paradigms: biopharmaceuticals versus low molecular weight drugs. *Int J Pharm.* 2003;266:3-16.
- Generic Biologics Bill Still Has Good Chance For Enactment This Year. *The Pink Sheet Daily.* September 7, 2007.
- Committee on Proprietary Medicinal Products. The European Agency for the Evaluation of Medicinal Products. Guideline on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance. Available at: <http://www.emea.europa.eu/pdfs/human/ewp/309702en.pdf>.
- Botox (Botulinum Toxin Type A) Purified Neurotoxin Complex package insert. Allergan Inc., Irvine, CA, January 2005.
- Wenzel R.G. Pharmacology of botulinum neurotoxin serotype A. *Am J Health-Syst Pharm.* 2004;61(suppl 6):S5-S10.
- Wenzel R, Jones D, Borrego JA. Comparing two botulinum toxin type A formulations using manufacturers' product summaries. *J Clin Pharm Ther.* 2007;32:387-402.

Exhibit 8: Most frequent Adverse Events

	Dysport®	Botox®
Blepharospasm	>10%	11%
Ptosis		
Cervicaldystonia		
Dyspnea	26%-39%	12.2-13%
Focal pain	11%	32%
Focal weakness	18%	17%
Cerebral Palsy		
Falls	7-8%	9.3%
Leg pain	8%	2.3%
Axillary HH		
Compensatory sweating	1-10%	4.5%

Most frequent adverse events for each product by overall incidence throughout the SmPCs analyzed

Reference: 10