# Meeting Report: AGA Biosimilars Roundtable

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In December 2017, the American Gastroenterological Association (AGA) Center for Diagnostics and Therapeutics (CDT) and the AGA Biosimilars Advisory Panel held a roundtable meeting in Washington, DC, to review the current and potential use of biosimilars in inflammatory bowel disease (IBD). This was a closed meeting with representation from clinical gastroenterology (adult and pediatric), the US Food and Drug Administration (FDA), the Crohn's and Colitis Foundation, a legal firm active in patent litigation in this area (Goodwin Procter), and 4 pharmaceutical companies with interest in the field (namely, AbbVie, Amgen, Boehringer Ingelheim, and Pfizer). Additional pharmaceutical companies were invited to participate but did not attend. This was a 1-day meeting with a brief introductory session on the preceding evening.

The CDT is the third of the AGA's specialty centers. Its recently revised mission statement is "To support the development of therapies and diagnostic tests that will enhance human health and improve the lives of patients with digestive and liver disorders." The CDT is overseen by a Scientific Advisory Board, whose current composition can be found online at www.gastro.org/cdt. The AGA Biosimilars Advisory Panel is chaired by Dr Gary Lichtenstein of the University of Pennsylvania and was established under the oversight of the CDT. The objective of this recent meeting was to bring together the relevant stakeholder groups in an effort to review the current state of the art and to determine educational priorities surrounding biosimilars for AGA members and their patients.

## Health Economics of Biologics and Biosimilars

Dr Lichtenstein reviewed the history of originator biologic agents and biosimilar agents in the treatment of IBD and other disorders, and some of the economic aspects pertinent to their development, introduction, and use. Patents protecting some of the originator biologic agents in IBD will be expiring within the next few years. There have been important technological advancements in manufacturing processes for biosimilar agents. Governments and third-party payers are under increasing pressure to control medication costs. Regulatory authorities have issued guidance statements about the use of biosimilars, and these agents have already been introduced into clinical practice in Europe, Korea, Japan, and Canada.

In the United States, the Biologic Price Competition and Innovation Act (BPCIA) was established in 2009 to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar to" or "interchangeable with" an FDA-licensed biological product. The FDA has approved 4 biosimilar products for use in IBD. The nomenclature of these agents comprises the generic name of the originator biologic agent followed by a suffix of 4 lower case letters. The suffixes are random and intended to be devoid of meaning. As of December 2017, the 4 approved biosimilar agents are infliximab-dyyb (Inflectra), infliximab-abda (Renflexis), adalimumab-atto (Amjevita), and adalimumab-adbm (Cyltezo).

In the European Union, authorization of biosimilars in IBD started in 2013; currently, there are 3 approved biosimilars for infliximab and 3 for adalimumab. The number of prescriptions for infliximab in the European Union (originator and biosimilar agents combined) has steadily increased since the availability of the biosimilar agents, but with the originator (Remicade) accounting for a smaller proportion of the total number (Figure 1). Biosimilars are now first line agents in several European countries. In the United States, depending on the penetration of biosimilar agents into the marketplace, there is the potential for substantial cost savings. Tumor necrosis factor monoclonal antibodies (infliximab, adalimumab, certolizumab pegol, and golimumab) currently account for about 64% of the total expenditure on biologic products. It is currently unclear how these potential cost savings will be distributed among insurers, infusion facilities, prescribers, and, most important, patients. Recent data have demonstrated use of biosimilars in Europe is cost saving.[1]

## Biosimilar and Interchangeable Products in the United States: Status and Key Development Concepts

Dr Leah Christl from the FDA reviewed current regulatory approval pathways for biosimilar agents. These agents are subject to an "abbreviated" development program that is

*Abbreviations used in this paper:* aBLA, abbreviated Biologics License Application; AGA, American Gastroenterological Association; APPs, advanced practice providers; BPCIA, Biologic Price Competition and Innovation Act; CDT, Center for Diagnostics and Therapeutics; FDA, US Food and Drug Administration; IBD, inflammatory bowel disease; RPS, reference product sponsors.


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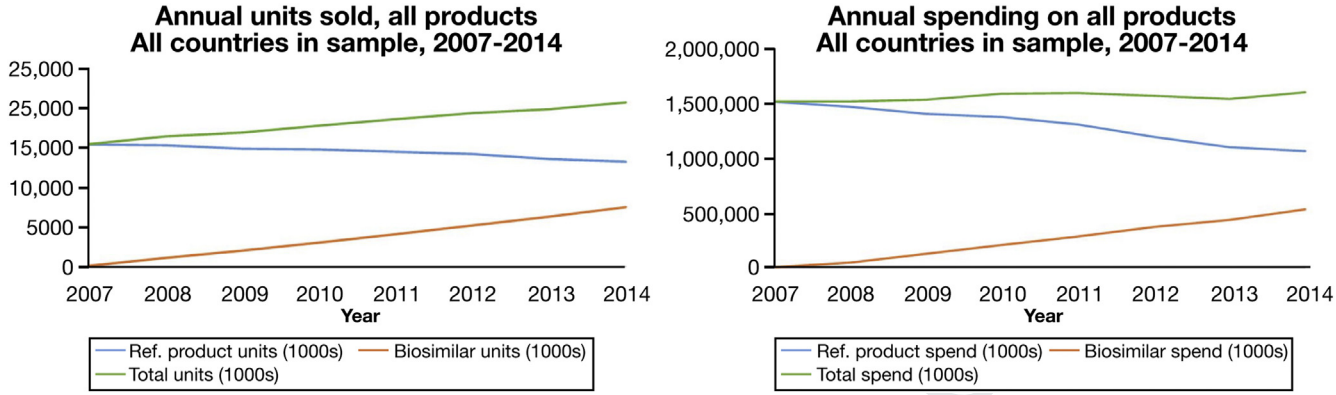


**Figure 1.** Sales and spending with uptake of biosimilars in 23 countries regulated by the European Medicines Agency. Reprinted with permission. (Morton FMS, Stern AD, Stern S. Harvard Business School Working Paper 16-141, 2016.).

designed to demonstrate biosimilarity (or interchangeability) to a reference product. She stressed that the abbreviated pathway does not imply a lower standard for the approval of biosimilar agents than for originator biological products. For approval of a biosimilar agent, analytical, nonclinical, and clinical studies are required to adequately demonstrate biosimilarity. Analytical data demonstrating extensive structural and functional characterization of the biosimilar product are fundamental to the approval process. The nature and scope of further clinical studies that would be required for approval depend on the level of any residual uncertainty about the biosimilarity of the 2 compounds after analytical characterization. A biosimilar product will have to demonstrate adequate pharmacokinetic similarity to the reference product and $\geq$1 study of potential immunogenicity is also required.

Based on the principle of extrapolation, a biosimilar product may be approved by the FDA for >1 indication for which the reference product is already licensed. (For example, a product demonstrating biosimilarity with an approved reference product and presenting clinical data in a rheumatologic condition could also be approved—by extrapolation—for use in IBD.) Key to the potential clinical application of biosimilar agents in IBD, however, is the concept of interchangeability.

Potentially, a patient being prescribed a reference product for IBD may be eligible (or may be required) to switch to an approved biosimilar agent (perhaps on the basis of cost savings). For a biosimilar agent to be considered "interchangeable" with a licensed, reference product, it must be expected to produce the same clinical result as the reference product. Furthermore, the risk to the patient of switching from one to the other must not be greater than the risk of simply continuing on the reference product. Risk includes both the safety and the potential for diminished efficacy of the biosimilar. Importantly for prescribers and their patients, an interchangeable product may be substituted for the reference product without the intervention (or—potentially—the knowledge or agreement) of the relevant health care provider (or—presumably—the patient). To support a demonstration of interchangeability, a switching study will be required. This study should be able to show that the risk of switching to the biosimilar—in terms of safety or of diminished efficacy over the reference product—is not greater than the risk of continuing on the reference product. Potential study designs of switch studies were discussed along with potential relevant study endpoints.

The FDA has prepared additional educational resources on biosimilars that can be obtained at www.fda.gov/biosimilars.

## Approval of Biosimilars in the United States: Approaches to Clinical Trial Design and Data Extrapolation

Dr Brian Feagan of the University of Western Ontario, Canada, discussed a physician's perspective and the evaluation of biosimilars in IBD. He stressed that biosimilars are not generic drugs in that they are not structurally identical to the reference product. These are complex protein structures with similar amino acid compositions. There are many types of post-translational modifications of these proteins that can occur. Common types of post-translational modifications include glycosylation (which includes galactosylation, fucosylation, high mannose derivatives, and sialylation), oxidation, phosphorylation, sulphation, lipidation, disulphide bond formation, and deamidation. Most of these chemical changes occur in vivo, but some may also occur in vitro. Changes to the proteins as a consequence of post-translational modification can lead to an alteration of the quaternary structure of these agents and subsequently modification of the protein activity, and can also influence the immunogenicity of these biosimilars when compared with the originators.[2–4] If a biosimilar agent is granted interchangeability status with a reference product and a patient undergoes multiple switches among the reference product and $\geq$1 biosimilars, there is increasing opportunity for the development of immunogenicity that may be associated with loss of effectiveness and clinical relapse. Because the development of antidrug antibodies to anti–tumor necrosis factor agents increases with continued use, there is the potential for the additional development of antibodies to biosimilar agents with possible subsequent loss of