



# BIOSIMILARS ACCEPTANCE: **Can Postmarket Research Change Roadblocks Into Runways?**

By Michele Cleary

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The abbreviated approval process for biosimilars leaves clinicians, payers, and other stakeholders with no product-specific clinical data to assess the safety and efficacy of the biosimilar product. Can real-world evidence fulfill the need for safety and efficacy data without eroding the cost advantages for biosimilars?

**B** iologics have revolutionized healthcare, bringing hope and relief to millions suffering from conditions ranging from cancer and multiple sclerosis to psoriasis and rheumatoid arthritis.[1] Yet these critically important advancements have come at a tremendous cost. Despite these products being used by only 1% to 2% of the US population, biologics account for 38% of the nation's prescription drug expenditures, accounting for 70% of the growth in drug spending between 2010 and 2015.[2,3] Biologics are consuming healthcare budgets at an unsustainable rate, forcing payers to make difficult choices regarding access and coverage. The complex development and manufacturing processes for biologics, coupled with small markets from which to recoup development costs, not only contribute to the hefty price tag but also nearly extinguish competition.[4]

### ENERGIZING MARKETS WITH BIOSIMILARS

Biosimilars have been heralded for bringing much-needed competitive pressure to the biologic market. These products are deemed to be “highly similar” to specific reference biologic products with *no clinically meaningful* differences with regard to safety, purity, or potency.[5,6] By providing comparable therapeutic benefit, biosimilars have the potential to lower prices within the biologic market at a time when drug prices are a national crisis.

Global regulatory bodies have recognized the need to encourage biosimilar development and to hasten their entry into the market. In the United States, the 2010 Biologics Price Competition and Innovation (BPCI) Act created the 351(k) approval pathway for biosimilars, an abbreviated pathway to approval by the US Food and Drug Administration (FDA). Under BPCI, sponsors need not re-establish the safety and efficacy of their biosimilar candidate, thus eliminating the need for extensive phase I-III trials.[7] Instead, sponsors can demonstrate their product's biosimilarity to its biologic reference product and thereby rely on the FDA's earlier determination of the reference's safety and efficacy. Once biosimilarity is established for one indication, the biosimilar can be approved for other indications through extrapolation. In other words, effectiveness is extrapolated to other indications without clinical data. Despite much debate about its validity, extrapolation provides a critical cost-savings mechanism to enhance market entry by biosimilars.

### THE ANEMIC ADOPTION OF BIOSIMILARS

Thus far, biosimilars have failed to affect the biologics market as previously hoped. While the FDA has approved 11 biosimilars, only 3 are currently marketed in the United States.[8] And these 3 have demonstrated only modest impact on the prices of reference biologics (price drops of 15%-35%).[9/12] While contracting and coverage issues have created market impediments from a payer perspective, survey data have shown that clinicians remain cautious about biosimilars, concerned about the lack of further evidence of the products' safety and efficacy.[13]. For stakeholders committed to evidence-based treatment decisions, extrapolation to an indication may be fueling prescriber skepticism and perhaps has slowed the adoption of biosimilars.

Recent surveys have revealed that many clinicians are uneasy with the FDA's abbreviated approval process for biosimilars and with

extrapolating to an indication without clinical data supporting a product's safety and efficacy.[13-15] A 2015 Quantia physician survey found that despite 94% of respondents viewing biosimilars as providing value to the healthcare system, less than 20% of prescribing specialists reported being “very likely” to prescribe biosimilars to eligible patients.[16,17] This reluctance appears to be due to residual concerns over the safety and efficacy of biosimilars, as many respondents voiced concerns about their safety and efficacy and shared that they were eager to review products' clinical data. The Biosimilars Forum found specialty physicians reported a similar desire for additional safety and efficacy information when considering a biosimilar, with 13% of respondents stating that they could not fully trust the FDA's assessments and that they would seek additional information before prescribing a biosimilar.[13] This survey found only 12% of respondents reported feeling completely comfortable with the concept of extrapolation, while more than one-third felt that an abbreviated approval process translates to a greater safety risk. These safety concerns were most prevalent among dermatologists and rheumatologists at 43% and 48%, respectively.[13]

Surveys also identified confusion among prescribers regarding when to introduce a biosimilar. A 2016 survey of specialty physicians found that these clinicians were more comfortable limiting biosimilars to their treatment-naïve patients rather than switching stable patients from a biologic to a biosimilar.[18] A reluctance to switch stable patients to a biosimilar was also identified in a separate 2016 study; only 1 of 8 rheumatologists surveyed said that they would switch a stable patient from a reference product to a biosimilar.[17] However, switching may be influenced by factors independent of treatment efficacy.

Physicians who choose to use biosimilars strictly in their treatment-naïve patients may have an easier time gaining patient acceptance than with patients who are stable on a reference biologic (payer step-care policies may also preclude this approach). Prescribers considering switching patients from a reference biologic to a biosimilar may require additional patient support to answer questions regarding why the change in treatment. Alternatively, a specific indication may influence the decision to switch when physicians treating more dire conditions (eg, cancer) may be less comfortable using a biosimilar with extrapolated indications.

Physicians have asserted that clinical trial data could improve their understanding of biosimilars and help them integrate biosimilars into their practices.[17] These survey data support further physician education initiatives that outline the differences between biosimilars and reference biologics, as well as the role extrapolation plays between the two. Physicians desire additional safety and efficacy data for biosimilars, as well as further research into treatment switching patterns. However, additional data on safety and efficacy could also help payers make informed decisions about coverage. Some hospitals and health systems may reserve biosimilars only for treatment-naïve patients or may require patients to fail first on the reference biologic—which makes it very unlikely that a biosimilar would be used.[19] In these cases, additional data on safety and efficacy, especially research into how switching impacts patient outcomes, may persuade payers to cover biosimilars on par with their reference biologics. >

## COULD REAL-WORLD EVIDENCE SPUR BIOSIMILAR ACCEPTANCE?

The abbreviated approval approach provides biosimilars with an important cost advantage by approving the products for indications through extrapolation rather than through extensive clinical trial data. Yet many stakeholders express unease with the lack of safety and efficacy data specific to the biosimilar product. While manufacturers could develop a research agenda of rigorous trials that could fill this data gap caused by extrapolation, doing so would also severely reduce or eliminate the cost advantage biosimilars bring to the market, eliminating whatever competitive pressure biosimilars impose on biologic prices. However, real-world evidence (RWE) may fulfill this need for further safety and efficacy data without eroding biosimilars' cost advantage. RWE could also provide important information on other lingering prescriber questions regarding optimal treatment outcomes for different subpopulations or whether switching leads to diminished efficacy. Luckily, multiple data resources exist to collect and analyze biosimilar RWE.

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The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) is a multistakeholder, nonprofit, scientific public service initiative that helps provide cost-effective postmarketing data. BBCIC utilizes Sentinel administrative data to monitor the safety and effectiveness of biosimilars and reference biologics, developing best practices for researching outcomes and methodologies for specific indications.[20] The group is currently considering expanding its data capabilities by including electronic health records, laboratory data, and patient- and clinician-reported outcomes in order to expand its analytic capabilities. Their input could be critically important to fill the information payers and providers need to inform their evidence-based decisions. Manufacturers could further disseminate BBCIC findings to plans and providers to reinforce/establish comfort with biosimilars' extrapolated results.

While BBCIC's Sentinel data analyses may be ideal for analyzing safety and efficacy of older biosimilars, the data lag associated with administrative claims data makes the Sentinel data inadequate for newly approved biosimilars (and those that have not hit the market). For newer biosimilars, international data would prove invaluable. To date, the United States has approved 11 biosimilars (only 3 of which have reached the market), while Europe has approved more than 40 biosimilars, with millions more years of patient exposure, since 2006.[21]

International data sources could provide a rich resource from which to analyze the safety and efficacy of biosimilar products in different patient subpopulations and for different indications. They can

also be a valuable resource to study outcomes in treatment-naïve patients versus those switched from a biologic. In addition, while there may also be interesting observations in terms of practice patterns and switching, other confounding factors could limit direct comparisons; differences in health systems may affect treatment choices differently. Yet the years of experience with these products could answer many stakeholder concerns about biosimilars both currently on the market in the United States and those soon to come onto the market.

To aid in these analytic efforts, ISPOR is starting a special interest group on biosimilars. ISPOR's biosimilar group may help develop postmarketing surveillance guidelines for biosimilars so that there will be sufficient information to address stakeholder concerns regarding biosimilar safety and efficacy without eroding biosimilars' cost advantages. This group may address how international data may be used to collect RWE on newer biosimilars; how to best study switching outcomes; and what are ideal reference groups for switching studies. This group will also incorporate a broad mix of stakeholders to not only provide the most accurate and relevant information but also to disseminate findings to ensure maximum and timely benefit.

## EFFECTIVE DISSEMINATION OF FINDINGS

Because many clinicians have lingering questions about the safety and efficacy of biosimilars, these clinicians are eager to learn more about the treatment outcomes associated with specific biosimilars before prescribing these products to their patients. Prior survey data confirm that both clinicians and patients become far more comfortable with biosimilars when they learn more about the products' safety and efficacy, and they are more likely to prescribe these products when equipped with these data.[18,22-24]

Disseminated data can also be incorporated into patient education materials to help counteract the barrage of direct-to-consumer advertising for reference biologics, while also mitigating patient nocebo effects, which has been demonstrated in clinical trials to negatively affect acceptance in patients switching from an originator product to a biosimilar.[25,26] Finally, payer stakeholders who determine formulary placement and reimbursement policies have significant control over how quickly biosimilars may be adopted into practice, and hence should be included in the first wave of data dissemination. Efficient dissemination of postmarketing data and analyses to all stakeholders will promote more rapid adoption of biosimilars into clinical practice. In addition, as biosimilars are more widely prescribed, the price-correcting competitive pressure from biosimilars will become more effective.

Since its launch of the Biosimilar Education and Outreach Campaign in October 2017, the FDA has taken a proactive role in educating healthcare practitioners, payers, and patients about biosimilars, their clinical benefits, and their potential value to patients. The Agency may be an effective partner in disseminating biosimilar research data. In addition to scientific journals and conferences, biosimilar data could also be shared with relevant specialty societies, as past surveys found that these societies were prescribing specialists' most trusted source of information on biosimilars.[27] Possible with input from BBCIC, the FDA, or the Biosimilars Forum, which provides evidence-based information

to inform and support public policies that encourage access and adoption of biosimilars, could also be employed.

Finally, while disseminating these postmarketing research findings, stakeholders may benefit from a review of the FDA's stance on the biosimilar approval process and extrapolated indications [7]:

“The abbreviated licensure pathway is not a lower approval standard for biosimilar biologic products. Rather, the abbreviated pathway allows for reliance on the FDA's previous finding of safety and effectiveness for the reference product, promoting a potentially shorter, or abbreviated, and less costly development program.

“Given the totality of the evidence approach and the scientific basis for extrapolation applied in the 351(k) licensure pathway, approval of a biologic product as biosimilar to a reference product means that patients and physicians can rely on the safety and effectiveness of the approved biosimilar product in the same way that they would for the reference product in each condition of use for which the biosimilar product is used.”

## BUILDING A MARKET FOR FUTURE BIOSIMILARS

Biosimilars have the potential to save our health system billions by injecting critical competitive pressure into the biologics market. Yet to influence prices in the market effectively, biosimilars must achieve sufficient market share. However acceptance of biosimilars has been slow due to persistent prescriber confusion and apprehension surrounding the safety and efficacy of the biosimilars.

Biosimilars can enter these markets thanks to extrapolated indications that require minimal clinical data. But this extrapolation process leaves payers, clinicians, and other stakeholders making evidence-based decisions with insufficient clinical data to fully support the use of biosimilars. Postmarketing analyses using either foreign or domestic data sources can provide the data necessary to quell any lingering doubts about safety and efficacy, while also informing best practices by indication and by patient type. These data will not only build stakeholder confidence in biosimilars, but they can also strengthen the biosimilar market sufficiently to ensure the entry of biosimilars long into the future. ●

## REFERENCES

- Chhina M. Overview of biological products. FDA Basics Webinar. June 17, 2013. Available at: <https://www.fda.gov/downloads/aboutfda/transparency/basics/ucm356666.pdf>. Accessed July 20, 2018.
- Coukell A. Specialty drugs and health care costs. Pew Charitable Trusts, Drug Spending Research Initiative website. <http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2015/11/specialty-drugs-and-health-care-costs>. Accessed July 23, 2018.
- Specialty drug spending. National Pharmaceutical Services website. [https://www.pti-nps.com/nps/wp-content/uploads/2017/04/NPS\\_SpecialtyMedication-White-Paper-Web.pdf](https://www.pti-nps.com/nps/wp-content/uploads/2017/04/NPS_SpecialtyMedication-White-Paper-Web.pdf). Accessed July 23, 2018.
- Isaacs JD, Cutolo M, Keystone EC, et al. Biosimilars in immune mediated inflammatory diseases: initial lessons from the first approved biosimilar anti-tumour necrosis factor monoclonal antibody. *J Intern Med*. 2016;279:41-59.
- Niederwieser D, Schmitz S. Biosimilar agents in oncology/ haematology: from approval to practice. *Eur J Haematol*. 2011;86:277-288.
- Wish JB. The approval process for biosimilar erythropoiesis-stimulating agents. *Clin J Am Soc Nephrol*. 2014;9:1645-1651.
- Dougherty MK, Zinch I, Christl L. Perspectives on the current state of the biosimilar regulatory pathway in the United States. *Clin Pharmacol Ther*. 2018;103(1):36-39.
- 2018 Biological Approvals. <https://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/ucm596367.htm>. Accessed July 23, 2018.
- Filgrastim-sndz. RED BOOK Online. Micromedex Healthcare Series [database online]. <https://redbook.solutions.aap.org/redbook.aspx>. Accessed July 20, 2018.
- Truven Health Analytics website. <https://truvenhealth.com>. Accessed July 20, 2018.
- Infliximab-dyyb. RED BOOK Online. <https://redbook.solutions.aap.org/redbook.aspx>. Accessed July 20, 2018.
- Infliximab-abda. RED BOOK Online. Micromedex Healthcare Series [database online]. <https://redbook.solutions.aap.org/redbook.aspx>. Accessed July 27, 2018.
- Cohen H, Beydoun D, Chien D, et al. Awareness, knowledge, and perceptions of biosimilars among specialty physicians. *Adv Ther*. 2017;(33):2160-2172.
- Ginestro M, Moore J. How to compete and win in a world with biosimilars: commercial launch strategies and defensive positioning for the US. KPMG International Cooperative. <https://home.kpmg.com/content/dam/kpmg/pdf/2015/10/world-of-biosimilars.pdf>. September 2015. Accessed July 20, 2018.
- Hemington A, Dalbeth N, Jarrett Pet al. Medical specialists' attitudes to prescribing biosimilars. *Pharmacoepidemiol Drug Saf*. 2017;May;26(5):570-577.
- Quantia. A roadmap for engaging physicians in the biosimilars discussion. August 2015. <http://www.businesswire.com/news/home/20150818005839/en/Quantia-Report-Reveals-Physician-Attitudes-Biosimilars>. Accessed July 20, 2018.
- Biosimilars in the US healthcare system: physician and access decision maker perspectives in 2016. Precision for Value website. [http://www.precisionforvalue.com/wp-content/uploads/2016/11/Precision\\_Biosimilar\\_Trend\\_Report\\_Sneak\\_Preview.pdf](http://www.precisionforvalue.com/wp-content/uploads/2016/11/Precision_Biosimilar_Trend_Report_Sneak_Preview.pdf). Accessed July 20, 2018.
- InCrowd. MicroSyndicated Study: Biosimilar Perceptions & Expectations. Published February 10, 2016.
- Woollett G. Use of step through policies for competitive biologics among commercial US insurers. Avalere website. <http://avalere.com/expertise/life-sciences/insights/use-of-step-through-policies-for-competitive-biologics-among-commercial-us>. Accessed July 20, 2018.
- Platt R, Carnahan RM, Brown JS, et al. The US Food and Drug Administration's Mini-Sentinel program: status and direction. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):1-8.
- European Medicines Agency, European Commission. Biosimilars in the EU: information guide for healthcare professionals. 2017. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Leaflet/2017/05/WC500226648.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf).
- Aladul MI, Fitzpatrick RW, Chapman SR. Patients' understanding and attitudes towards infliximab and etanercept biosimilars: results of a UK web-based survey. *BioDrugs*. 2017;31:439. <https://doi.org/10.1007/s40259-017-0238-1>.
- Jacobs I, Singh E, Sewell KL, Al-Sabbagh A, Shane LG. Patient attitudes and understanding about biosimilars: an international cross-sectional survey. *Patient Prefer Adherence*. 2016;(10):937-948.
- Smastuen MC, Brandvold M, Andenaes R. Is patient satisfaction with being switched to a biosimilar medication associated with their level of health literacy? Results from a Norwegian user survey. *Ann Rheum Dis*. 2018;77(suppl 2):86.
- Rezk MF, Pieper B. To see or NOsee: the debate on the nocebo effect and optimizing the use of biosimilars. *Adv Ther*. 2018 Jun 5. doi: 10.1007/s12325-018-0719-8.
- Tweehuysen L, van den Bemt B, van Ingen IL, et al. Subjective complaints as the main reason for biosimilar discontinuation after open-label transition from reference infliximab to biosimilar infliximab. *Arthritis Rheumatol*. 2018;70(1):60-68. doi: 10.1002/art.40324.
- Manolis CH, Rajasenan K, Harwin W, McClelland S, Lopes M, Farnum C. Biosimilars: opportunities to promote optimization through payer and provider collaboration. *J Manag Care Spec Pharm*. 2016;22(9-a suppl): S3-S9.

### About the Author:

Michele Cleary is an HEOR researcher and scientific writer with more than 15 years of experience in the healthcare field.

### Additional information:

For more information on ISPOR and biosimilars, contact [sigs@ispor.org](mailto:sigs@ispor.org).