EDITORIAL

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Biosimilars for Healthcare Professionals

Biosimilars: patient and physician acceptability is the fifth hurdle to market competition

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Biosimilar products confront novel market authorization and post-marketing use hurdles. Existing evidence is insufficient to fully address physician and payer acceptability thresholds.

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In this issue of *GaBI Journal*, Sandorff et al. [1] investigate payer and physician views on biosimilars' interchangeability and discount thresholds in three Latin American countries. It contributes to our understanding of when physicians and payers may perceive biosimilars to be sufficiently safe and economically attractive. Their finding that trust in the regulatory authority is a crucial factor should be considered when investigating interchangeability and discount thresholds in other nations.

Biologicals offer new therapeutic alternatives for many, yet cost threatens their broad acceptance. Lower-priced biosimilars, however, may increase the availability of these therapies. Experience with biosimilars shows that physicians will be reluctant to prescribe them and patients reticent to use them if: (i) they lack trust in the science behind the safety and interchangeability evidence required by regulators, and (ii) the cost differences between the biosimilar and the reference listed product is too small.

Unlike generics competitors who make small molecule products, biosimilar manufacturers face hurdles to marketing and use beyond demonstrating safety, efficacy and quality. Post-marketing, there is the now familiar expectation of cost-effectiveness evidence. Determining the value both of biological and of biosimilar products is less direct than it is for small molecule products. Yet this *de facto* fourth hurdle determines whether and to what extent a product is included in a pharmaceutical benefits scheme. Existing evidence is insufficient to meet governments', private entities', patients' and manufacturers' needs to understand safety, interchangeability, cost/value and acceptability comparisons before and after marketing authorization. Additional methodological development is required to assure the rigour and the comparability of clinical and economic studies of reference listed products and biosimilars.

Cost-effectiveness and value in the marketplace have different meanings in different national contexts, particularly when the perspectives from which the analyses are performed shift. The global marketplace is granular – findings in one nation (or state) may only be suggestive in another. Demonstration of value from a large central government perspective versus that from a fragmented and predominately market-based approach result in different calculations and, subsequently, differential diffusion of products to patients.

Europe has extensive experience with evidence generation for biosimilars, but the United States has lagged in market authorizations. Healthcare reform in the US addressed this by including the Biologics Price Competition and Innovation Act [2], which set the policy that *the sense of the Senate* [is] *that a biosimilars pathway balancing innovation and consumer interests should be established* and noted that such products refer to those which are *highly similar*. Implementing this requirement is occurring through a series of guidances [3, 4] on safety standards, biosimilarity (or interchangeability) and product exclusivity. This pathway has rapidly elicited a US market response with (65) biosimilar products either in clinical trials (23) or that had begun discussions (42) [5] by June 2014. The US Food and Drug Administration approved the first biosimilar (filgrastim-sndz) for marketing on 6 March 2015 [6].

Over the 10-year period 2014–2024, direct savings in the US attributable to the use of biosimilars is estimated at US$44.2 billion [7]. There are strong assumptions in this and similar estimates offered by others. Even when biosimilars have established safety, effectiveness, quality and cost-effectiveness, an additional hurdle of clinician and patient acceptability remains. Results from one nation, however, are not directly generalizable to others due to differences in national practice patterns, extent of public–private involvement in the healthcare system, payment schemes, patient values, and regulatory apparatus.

Patients are increasingly important as payers. Out-of-pocket cost sharing by patients can be substantial, depending on the social or private health insurance programmes in which they are enrolled. Such financial concerns compete with physician, payer and patient requirements for interchangeability and product safety. Exclusion of a marketed product from a pharmaceutical benefit or inclusion that requires substantial patient cost sharing may significantly constrain a product's use. If patients decline to fill or to refill a prescription then there is no utilization. In the absence of evidence, speculation and guesses about patient and physician preferences are unsystematically weighed with biosimilars' potential price discounts. The main goal of evidence-based decisions is to avoid such anecdotal approaches.

The opportunity with biologicals and biosimilars is substantial – it is displacing small molecules in terms of resource investment and consumption – yet current methodologies and evidence are insufficient.

When Americans began to enroll in the US managed care plans by the millions, there was insufficient economic impact evidence then to guide health plans and payers in

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designing competitive insurance benefits for pharmaceutical products. Elixhauser et al. quantified the surge of peer-reviewed economic impact studies to meet that growing demand in two separate periods pre-dating and spanning the enrolment experience (1979–1990 [8] and 1991–1996 [9]).

Though numerous, clinical publications at the time did not provide strong research guidance for clinical practice. In the 1980s, Eddy et al. reported on variations in medical practice [10] and shortcomings in the quality of medical evidence for clinical decisions [11]. Subsequent developments have advanced the science of clinical research, evidence synthesis and guideline development, such as the Cochrane Collaborative and the Cochrane Database of Systematic Reviews [12].

Similarly, we are at an early stage of evidence development for biosimilars and the need now is at least as great as it was for information on pharmaceuticals in the previous generation. Governments, private entities, physicians, manufacturers and patients require high quality clinical, regulatory and economic information to perform their roles effectively. Decisions about the hurdles for marketing and diffusion of new products require safety, efficacy, quality, cost-effectiveness and now acceptability information. Sandorff et al. [1] provide insights for this fifth hurdle in three Latin American nations.

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