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# A patient-centred paradigm for the biosimilars market

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The advent of similar biological medicinal products or 'biosimilars' in Europe in the 2000s has led to development of a global biosimilars market and regulatory frameworks designed specifically for approval of biosimilars. Like originator biologicals, biosimilars exhibit greater molecular complexity than small-molecule drugs, including generics. Current estimates suggest that biosimilars are more expensive and require longer development times than generics. Regulatory and industry conferences have addressed how to achieve the appropriate level of regulation for biosimilars. Many originator biologicals feature support programmes or additional services that are designed to improve usage by patients, prescribers, and payers; these are not a mandatory part of the regulatory approval process. We refer to these features collectively as the 'biologicals experience' as described and discussed in this paper, and suggest that this experience should be an important element of consideration for the development of public policies on biosimilars.

**Keywords:** Biosimilars, medical devices, patients, prescribers, public policy, outcomes

## Introduction

In the history of medicine, biologicals are relatively new products. Biologicals developed in the 1980s produced an impact in nephrology, oncology, and other therapeutic areas. The expiration of intellectual property rights on originator biologicals created the possibility for development of 'follow-on biologic' products, based on the originators. The EU in 2005 initiated public discussion on guidelines for approval of such products [1], which it denominated as 'similar biological medicinal products' in the guideline but also referred to as 'biosimilars' in subsequent publications [2]. EMA approved its first biosimilar under these guidelines in 2006. Since then, many countries on all continents (besides Antarctica) have adopted similar biosimilar regulatory approval procedures, and the WHO has developed a guideline for development of such regulatory guidelines. Regulatory and industry conferences have addressed how to achieve the appropriate level of regulation for biosimilars [3]. One consulting company recently estimated the combined annual growth rate of the global biosimilars market at 52% for the time period 2010–15 [4].

## Special challenges for biologicals and biosimilars

Biosimilar manufacturers face unique manufacturing, financing and developmental challenges. As with all biologicals, biosimilars are more structurally complex than small-molecule drugs [5]. Biologicals, including biosimilars, are produced through means which will almost always differ by manufacturer: cell lines, mass production and purification processes, and even issues like temperature and availability of light within a manufacturing facility [6]. The average capital cost for development of a biologicals manufacturing facility is US\$250 – US\$450 million [7].

Many state-of-the-art techniques are evolving to help characterise biologicals, but cannot yet demonstrate biopharmaceutical equivalence [8]. In the EU and WHO guidelines, biosimilar manufacturers have to demonstrate comparable quality to an originator biological and usually also need a non-clinical and clinical research programme that also demonstrate comparability. This will usually include a phase III clinical trial. A biosimilar manufacturer also cannot benefit from regulatory data protection. Even though it must generate its own data to submit to regulators, most regulations preclude the use of a biosimilar as

a reference product [9–11]. Overall, these challenges amount to long development timelines (5–8 years) and overall development costs of US\$100 – US\$200 million [2].

A potential challenge for the future could concern interaction with physicians and the use of sales representatives to provide information on biosimilars [12]. In the EU, some companies have used sales representatives, but this is a cost not normally associated with the generics industry. The Generic Pharmaceutical Association has expressed concern to FDA that manufacturer promotional efforts might result in a 'detailing war' [13].

## The biologicals experience

In addition to the manufacturing, research and development challenges for bringing a biosimilar to market, competitive challenges exist when on the market. Although price can be one area of competition [14], originator biologicals often provide a number of supplemental services and programmes that support patient comfort, prescriber concerns, and payers' desires for proper reimbursement procedures. These services, which we call collectively the 'biologicals experience', are not mandated by regulators but can be meaningful to patients, prescribers, and others.

## Patient-related aspects

- **Devices:** most biologicals come with some kind of delivery device. The mode of delivery has an impact on how patients feel about the medicine and what they can expect [15]. For people with severe rheumatoid arthritis, for instance, auto-injection devices need to be user-friendly for people with limited dexterity [16]. Patients may also need expert training with the devices in order to achieve the right outcomes.
- **Patient support systems:** handling patient concerns is especially important for originator biologicals and biosimilars. Systems need to be in place to sort out potentially important adverse events from administration errors or routine questions. Some manufacturers provide telephone lines with dedicated nurses for patients. Considering general consumer frustration with anonymous call centres [17], the quality of the patient support system will be integral to supporting patient comfort and confidence.

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- *Replacement systems*: for retail products, replacement can be a crucial issue, especially if a needle breaks or another quality deficiency is found. Companies will need to develop mechanisms that can get the right replacement to patients in time to address their needs.
- *Naming*: names of biosimilars will be very important for patients. On the one hand, names will need to be distinct for tracking and tracing purposes, especially when there is a need to distinguish the exact biological product that triggered an adverse event report. On the other hand, they will need to be similar enough to the originator to provide a high level of confidence. Since WHO's international nonproprietary name (INN) policy does not provide a basis for distinct INN for all biologicals, these issues can be resolved by companies through development of similar but distinct trade names [18].
- *Access programmes*: some originator programmes ensure that cost will not be an obstacle to biologicals access for patients. This goal can be achieved through direct financial support or support to patients with reimbursement programmes.

**Prescriber-related aspects**

For prescribers as well, biologicals present a very different experience. Infusion-administered biologicals require dedicated facilities and extra staff time, as well as specialised rooms for administration to patients. The cost for biologicals is quite high and can pose cash flow concerns for smaller practices.

- *Physician education*: originator biologicals companies have been educating physicians for years [19] about their products, and biosimilar companies have only recently started similar efforts in Europe. Research by the National Comprehensive Cancer Network indicates that 'familiarity with biosimilars is suboptimal and that more clinician education is required' [20]. Education for nurses has also been identified as an area of need [21].
- *Physicians' need for clinical data*: a recent report indicates that the data necessary for marketing authorisation might not suffice for the needs of prescribers. Both payers and prescribers indicated they would want to see additional data on efficacy for biosimilars in order to encourage their uptake [22]. This need is even more pronounced when considering whether a manufacturer can extrapolate from the primary approved indications to others.
- *Physician reimbursement services*: originator biologicals manufacturers often provide support services for physicians and practices to ensure proper reimbursement decisions [23-25]. Reimbursement rules often dictate when patients can receive the biological, and the biological needs to be present in the exact right amount at the right time [26]. A biosimilar manufacturer that failed to offer this kind of support would have extra difficulty in presenting itself as an attractive option for specialty practices or others who rely on such services.

Another important stakeholder group for biologicals is the payer community, which has to manage the costs of originator biologicals. Patients' adherence to biologicals is not well researched and a review of rheumatoid arthritis studies suggest that better methods are needed for tracking patients and prescriptions as well as for devising appropriate interventions [27]. Having said that, Blue Cross Blue Shield of North Carolina, USA, has set out to improve adherence for biologicals by developing patient-centred interventions [19]. According to Dr Marissa Blum of Temple University, Philadelphia, USA, in many ways, adherence

boils down to the individual patient-provider relationship [19]. To the extent that further research identifies elements of the biologicals experience that improve or sustain adherence, those elements could help payers avoid unnecessary costs from non-adherence.

It should be noted that the individual factors below also can pertain to some small-molecule drugs, especially structurally-complex ones or those involving devices. Patients' usage of asthma inhalers, for instance, received attention by *The New York Times*, when a widespread shift in the inhalation devices impacted patient behaviours [28]. Generic injectables have also been the object of recent attention owing to shortages in the US [29]. We would not argue that each individual factor is specific solely to biologicals, but that biologicals generally possess many of these features in a way that supports the patient and prescriber's overall experience with the medicine.

This list is hardly exhaustive, but gives insight into the manifold elements in the biologicals experience that can support optimal health outcomes for patients.

**Case study: device improvement**

The case of Omnitrope (somatotropin) illustrates how commercial success can relate to the biologicals experience. Omnitrope, which was the first biosimilar approved in 2006 by the EU, initially experienced minimal uptake. While the fragmented marketplace appears to have been a key factor [30], much of the blame can also be attributed to the delivery device. In the first Omnitrope delivery system, the multi-step mixing of the Omnitrope and measuring of the dosage were two phases of the process that were much more complex than predicate systems, and discouraged uptake and patient adherence [31].

The manufacturer subsequently initiated a switch from a 'lyophilised powder form in a vial' [32], to injector pens 'Omnitrope Pen 5 and 10, with liquid cartridges in 5 mg/1.5 mL and 10 mg/1.5 mL strengths' [33]. These new systems represented increased convenience for patients because 'the liquid is already dissolved in a ready-to-use cartridge and can be loaded into the pen for injection' [33].

With the implementation of the new delivery system, the manufacturer experienced increased sales. Executives have claimed that the new device represents a 'commitment to meeting the needs of patients through providing more convenient delivery systems' [34], as well as its commitment to a fundamental business strategy of 'focus on difficult-to-make products that provide added patient benefits' [35].

**Discussion: policy implications**

Many meetings of regulators and industry officials have taken place since the first EMA consultations in 2005. Most recently, FDA held a public session in November 2010 [36] and EMA held a consultation on monoclonal antibodies in October 2011 [37]. Numerous other industry conferences have been organised by private-sector vendors [38].

Written comments submitted to FDA after the November 2010 consultation provide insight into a wide variety of issues, based on questions posed by FDA [38]. Many of the regulatory policy

issues posed by FDA focused on criteria for regulatory approval of biosimilars: use of foreign reference data, factors to assess similarity, and others. By and large, these issues pertain to the question of how to obtain marketing authorisation.

The issue of interchangeability, however, has great relevance for the 'biologicals experience'. The US Biologics Price Competition and Innovation Act (BPCIA) of 2009 allows an applicant for a biosimilar marketing authorisation to further seek designation as an interchangeable product, which would facilitate pharmacy-level substitution where allowed by state law. 'The BPCIA requires the FDA to deem a biosimilar 'interchangeable' if the biosimilar 'can be expected to produce the same clinical result as the reference product in any given patient' ... 'The question of whether an interchangeable biosimilar should be automatically substituted will remain one of state law' [39].

In its written comments to FDA, the Generic Pharmaceutical Association in the US argued that 'FDA needs to understand that interchangeability is the engine that most immediately drives competition and supports access through affordability' [13]. Likewise, a consultant for the Parexel consulting company has publicly claimed that interchangeability would be a critical factor for a biosimilar's commercial success: 'the fact is, you need interchangeability in the label to succeed' [40].

Outside the US, global regulatory policy offers little guidance on this issue. The EU, WHO, Canada and Japan do not provide an approval pathway for interchangeability as part of the marketing authorisation process [41]. Malaysia proscribes automatic substitution, and Saudi Arabia says it is 'not encouraged' [42, 43]. While it is possible that FDA or another regulator will develop a test for interchangeability in the future, FDA itself has expressed concern over the limits of determining it via current scientific methods [44]. As Health Canada has noted, significant clinical trial work would need to be undertaken, but such studies are unlikely in most situations [45].

Policy issues on interchangeability are complicated by the different settings in which biologicals are sold. Many biologicals are administered at specialty practices or at hospitals. In these situations, the issue of substitution by pharmacists is less significant, because the practices or hospitals will likely make joint decisions about ensuring availability of a limited number of biologicals. In this setting, prescribers would be part of the decision-making process and could work with their patients to manage key aspects of the biologicals experience [46].

One area for further discussion, however, should focus on how interchangeability policies would affect the biologicals experience. If the primary beneficiaries of the biologicals experience are indeed patients and prescribers, how will their interests and voices be heard in this process? If a pharmacist can substitute a product with a user-friendly device for one with a less user-friendly device, what recourse does a patient have? What are the risks to eliminating elements of the biologicals experience?

We would suggest that a focus on optimal outcomes for patients should be a high priority for policymakers who might encounter this issue. Such an approach would entail consideration of the facets of the biologicals experience that have the

most relevant impacts on health outcomes. And we believe that such an approach would ultimately strengthen support for policies that preserve the ability of the physician to choose the best biological for an individual patient—whether that is an originator or a particular biosimilar.

To encourage further savings, policymakers can eliminate market access barriers in order to incentivise biosimilar manufacturers to enter markets. Transparency in expectations for health technology assessments (HTA), for instance, could give meaningful guidance to biosimilar manufacturers, since the use of 'often-inappropriate methodology creates a very real chance that HTA authorities will reject some biosimilars' [47]. In Europe, many manufacturers face long delays by Member States for reimbursement approval [48]; in the case of lower-cost biosimilars, such delays would actually postpone potential savings for the Member States.

## Conclusion

The entry of biosimilars into the European and other markets in the last decade has been facilitated by the development of regulation designed for unique aspects of biologicals. To meet the demands of this regulation, companies must overcome financial and technical challenges that are not present for small-molecule generic drugs. Beyond regulatory approval, however, originator manufacturers' support services provide a 'biologicals experience' that can be important to patients and prescribers. While this experience poses a further challenge for biosimilar manufacturers, it also provides an opportunity to optimise these lower-cost products for patients. Public policies related to interchangeability and pharmacy-level substitution thus need assessment not only of their scientific grounding, but also of the potential impact of such policies on the biologicals experience and thus on outcomes for patients themselves.

## For patients

This paper proposes that public policies on biologicals and biosimilars take into account the 'biologicals experience', the variety of support services and programmes provided by originator manufacturers to support patient and prescriber use of existing biologicals. Patients should expect that evaluation of interchangeability and pharmacy-level substitution policies would focus not only on minimising costs but also on ensuring optimal health outcomes.

## Disclosure

Dr James N Class is Director of Global Public Policy at Merck US. Ms Lauren Langis is Global Policy Co-Op at Merck US. This article represents the views of the authors and is not necessarily representative of Merck's public policy views.

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