

## **An overview of biosimilars**

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### **Abstract**

Biologics have become an increasingly important but also expensive part of the global medicinal cabinet. Generics of this class of drug, termed biosimilars, can relieve the financial burden on healthcare systems and improve patient accessibility. This mini-review covers the evolving international regulatory legislation for biosimilars, challenges for biosimilar development and expected developments.

### **Keywords**

Biosimilars, biologics, regulatory guidelines, safety

### **Introduction**

Biopharmaceuticals or biologics have revolutionised medicine, advancing the treatment of diseases from rheumatoid arthritis to cancers. Over the last decade, they have experienced an explosive growth and now account for an astounding 30% of global pharmaceutical research and development spending (McCamish et al. 2012). In 2012, five of the top 10 global best-selling prescription drugs were biologics (Lindsley 2013), and sales of this class of medication are expected to reach USD 150 billion worldwide by 2015 (Butler et al. 2012). In turn, biologics are expensive and expend enormous portions of government healthcare budgets. For example, in the US, 50% of the charges for the top 20 drugs in outpatient oncology clinics are for biologics (Hirsch et al. 2013).

‘Generic’ biologics, defined as a copy of an existing approved biologic with demonstrated similarity in physicochemical characteristics, efficacy and safety (Weise et al. 2011), are therefore much sought after to relieve healthcare costs and increase access to treatment (Roger 2010).

Generics of small molecule drugs enter the market rapidly after patent expiry of the original pharmaceutical, leading to robust competition and significant cost reductions to patients. However, unlike small molecule drugs, the development of ‘generic’ biologics is not straightforward. Biologics are a pharmaceutical drug class that is defined by their production in living systems, such as bacteria or mammalian cells. The majority of biologics are proteins and thus entail a

complex manufacturing process. The primary steps involve the cloning of the relevant gene into a complementary DNA (cDNA) vector, which is then transferred into a host cell (typically from *Escherichia coli*, yeast or Chinese Hamster ovary cells) (Dranitsaris et al. 2011). An optimal cell-line is chosen, then expanded and purified into the bulk drug for validation and quality control processes (Papp et al. 2013). These manufacturing techniques and cell lines are typically proprietary, and the complexity of these molecules makes development of ‘generic’ biologics significantly more expensive than for small molecules (Casadevall et al. 2013).

Additionally, the large number of process variables, lack of access to the original cell line and the sensitivity of biologics to manufacturing conditions, means that ‘generic’ biologics are unlikely to completely replicate the reference product. Thus ‘generics’ of biologic drugs are appropriately termed biosimilars, as they are likely to contain some structural or functional differences (Kanter et al. 2012, Ebbers et al. 2012). Whilst these molecular differences may not be detectable with existing technology, they can have potentially important impacts on the safety and efficacy of the drug (Papp et al. 2013). Thus the definition of a biosimilar is further defined as being highly similar to the innovator product, notwithstanding minor differences in clinically inactive components (Konski 2011). Whilst the standard approach for generic small molecule drugs consists of comparative bioavailability studies, these are inadequate for bringing a biosimilar to market. Rather, comprehensive comparability analyses with the reference biologic are generally required, which contribute to the cost of development (Weise et al. 2011).

The first biosimilars became available with the “Guideline on similar biological

medicines”, which was introduced in the European Union (EU) in 2005 (Dalgaard et al. 2013). Whilst a number of biosimilars have since become available, including 14 in the EU (Dranitsaris et al. 2011), their market penetration has been relatively slow. For example, in Denmark, biosimilars of Filgrastim have gained less than 10% of the market (Hirsch et al. 2013). However, an unprecedented opportunity for rapid growth of the biosimilars market is fast approaching, with 12 patents for biologics expiring before 2020 (Pani et al. 2013). Indeed, the worldwide market for biosimilars is expected to grow to USD 3.7 billion by 2015, from just USD 243 million in 2010 (Konski 2011). The future potential for biosimilars is even greater, with more than 100 original biologics in current clinical use and many more under development (Roger 2010).

Nonetheless, biosimilars continue to face regulatory and commercial uncertainties, which are discussed below.

### **Current legislation and regulatory guidelines**

Clear regulatory guidelines for biosimilars are essential for both manufacturer investment and acceptance by clinicians and patients. In general, international regulatory bodies agree that standards for approval of biosimilars differ from those for small molecule generics, and typically emphasise the need for direct analytical and biological comparison to the reference biologic (Papp et al. 2013). Additionally, rigorous post-approval pharmacovigilance programs are mandated to rapidly identify any serious adverse effects (Dranitsaris et al. 2011). Nonetheless, the requirements are less than for a new biologic and an abbreviated approval pathway is defined, though at the current time of writing, there is no single uniform international

guideline for biosimilars. Rather, there is a dichotomy of a highly regulated and a less regulated registration pathway. Existing global regulations have been extensively reviewed by Konski et al. (2011) and Dranitsaris et al. (2011).

### **Highly regulated approval pathways**

#### *European Medicine Agency (EMA)*

Since the release of the initial “Guideline on similar biological medicines” in 2005, the EMA has continued to be at the forefront of legislation governing biosimilars and a standard for regulatory authorities in other countries. Current guidelines are well-defined, and address major concerns including safety, immunogenicity, clinical efficacy and the extrapolation of indications. Additionally, the material is tailored to specific classes of biosimilar agents, such as erythropoietin, insulin, growth hormone, low molecular weight heparin and interferon alpha (Dranitsaris et al. 2011). This is necessary as the complex characteristics of biologic molecules means that a ‘one size fits all’ assessment of biosimilarity is inadequate (Kozlowski et al. 2011). Interestingly, the EU guidelines do not discuss the issue of interchangeability or automatic substitution of biosimilars for the original drug as this is decided by individual EU nations. (Weise, 2011).

A criticism of the EMA position on biosimilars is its emphasis on clinical proof of similarity, which has been a deterrent to some biosimilars applicants. Following significant improvements to analytical characterization techniques over recent years, the EMA has indicated that it may begin to increase reliance on analytical data (Senior 2013). Kozlowski et al. (2011) commented that clinical requirements may eventually be reduced as analytical techniques eventually will allow for extensive use of “fingerprint” comparison

between a biologic and biosimilar. This resulting cost-savings of biosimilar development might then be passed on to the patient. However, animal and clinical studies will still be required in the near future to provide adequate early safety and efficacy data (Kay 2011).

#### *US Food and Drug Administration (FDA)*

In 2009, US congress passed the Biologics Price Competition and Innovation Act (BPCIA) as part of Patient Protection and Affordable Care Act, which empowered the FDA to identify an abbreviated approval pathway for biosimilars (Kozlowski et al. 2011). Prior to this, the FDA already had indirect experience evaluating biologics and biosimilars (McCamish et al. 2012). Firstly, new drug applications for biologics via the FD&C Act whereby biosimilars could follow an approval pathway similar to that of small molecules. Secondly, via comparability testing that are enforced when any manufacturing process changes are made for original biologics (e.g. scale-up and modernizing the process). Given this prior knowledge and the detailed European experience and guidelines, the US approach to the approval process for biosimilars can be greatly accelerated. However, it appears from previous meetings with stakeholders, that the FDA is unlikely to directly adopt the EMA guidelines (Dranitsaris et al. 2011).

In 2012, the FDA issued draft guidance documents that included scientific and regulatory considerations for biosimilar applicants (Papp et al. 2013; Casadevall et al. 2013). Interestingly, the FDA guidelines provision for the interchangeability or automatic substitution of biosimilars (Weise, 2011). However, unlike small molecule drugs, frequent interchanging of biologics can compromise the safety and efficacy of the

medication, potentially leading to severe immune reactions. The FDA has yet to determine the data necessary for such a designation, and only experience over time will determine the extent and validity of biosimilar interchangeability (Kay 2011), Kozlowski et al. 2011).

#### *Other countries*

A number of other countries have followed the highly regulated pathway, with requirements based on the EMA guidelines.

The Canadian food and drug regulatory agency (Health Canada) has termed biosimilars as ‘subsequent entry biologics’, which are treated as a new drug submission. Direct substitution or interchangeability is not permitted and guidance is for specific drug classes only (Papp et al. 2013, Dranitsaris et al. 2011). At this time, only a single biosimilar (Omnitrope, containing the human growth hormone somatropin) has been approved (Papp et al. 2013). The Canadian guidelines are discussed in detail by Papp et al. (2013).

The Australian Therapeutic Goods Administration (TGA) has also adopted the European guidelines for approval of biosimilars. Because biosimilars will be assessed on a case-by-case basis, a pre-submission meeting with the TGA is encouraged for manufacturers to determine data requirements. Omnitrope has been approved for use in Australia since 2006 (Roger 2010, Dranitsaris et al. 2011).

#### **Less regulated regulatory pathways**

In some countries, approval criteria for copies of original biologics are less stringent to accelerate their potential for cost savings. For coherence of the manuscript we describe these as biosimilars. However, the less rigorous comparative assessments in these countries have seen them referred to as a

‘biopharmaceutical not subjected to regulatory approval’ (Roger 2010). Nonetheless, in China and India, this approach has resulted in a wide range of these less regulated biosimilars being available or under development (Dranitsaris et al. 2011). However, the guidelines for them are relatively vague.

#### *China*

China’s biosimilar law, which is regulated by State Food and Drug Administration (SFDA), states that a biosimilar product must be registered and approved as a new biological product. This is regardless of whether the originator drug is commercially available in the Chinese market. Whilst a biosimilar may be given an abbreviated approval process, this appears to be implemented and defined at the discretion of the SFDA (Konski 2011).

#### *India*

In contrast, Indian regulations do not have a defined biosimilars category. Rather, any biosimilars of a biologic that have been on the market for more than four years undergo an abbreviated approval pathway, whilst biosimilars of newer biologics must register as a “new” product. Additionally, the Drug Controller General appears to be the primary regulatory authority but approval from other agencies is also possible (Konski 2011).

### **Commercial Outlook**

Commercial success of biosimilars is dependent on a number of challenges that have seen the relatively slow uptake of biosimilars compared with small molecule generics. There is a need to develop more effective approval pathways that provide adequate market incentives for biosimilar companies, whilst maintaining a balance with measures that ensure patient safety. Failing these, it is likely that companies will simply

shift their focus to developing ‘bio-betters’ (improved versions of an existing biologic) or new biologics. In this scenario, without the cost suppression from biosimilars, prices of biologics will remain high and limited patient accessibility will continue (Kanter et al. 2012).

A crucial aspect is the pricing of biosimilars. Biosimilars will not see the same level of discounts as generics of small molecule drugs, because of greater upfront costs associated with an expensive development and approval process. Whilst small molecule generics might be priced 80% lower than the brand name, biosimilars are likely to be priced at a lesser 20 to 40% discount (Senior 2013, Hirsch et al. 2013). However, we expect this discount will be greater in countries requiring less stringent regulatory steps, and as analytical technologies improve and the requisite for *in vivo* data is reduced (Senior 2013). Another challenge is that manufacturers of originator biologics may cut their prices to remain competitive and thus are capable in retain their significant market share (Hirsch et al. 2013). As price is the main driving factor, it is much more difficult for biosimilars to penetrate the market than traditional small molecule generics.

Just last year, McKinsey & Company (2013) published a white paper on the future of the biosimilars market. They commented that recent changes to develop more streamlined guidelines in emerging markets, particularly in the Central and South American nations, will permit companies to develop effective regional strategies for biosimilars. Additionally, incentives to boost local biosimilar development are evident, for example, in a biotech consortium of Brazilian pharmaceutical companies, as well as the Chinese government’s investment in local biotech companies and partnerships with multinational biologics companies. This is coupled with relatively low degree of patent

protection in countries that have much smaller investments in original biologics, such as China and India (Table 1), who already have less expensive approval processes (Konski 2011). Table 1 shows the length of market and data exclusivity for original biologics. Data exclusivity describes the period during which any safety or efficacy of the original biologic cannot be used for comparison and thus the period during which regulatory authority will not accept new applications for a biosimilar. Entry into emerging markets may therefore be a valuable opportunity for biosimilar manufacturers, both as a source of early revenue and accumulating data for approval processes in more regulated countries.

However, safety concerns remain a barrier to greater acceptance of biosimilars. All biological products have the potential to cause immunogenicity, which can be life-threatening (Patel et al. 2014). However, even with recent advances in *in vitro* and complex *in vivo* models, these cannot always be predicted (Calo-Fernandez et al. 2012). There are well-documented examples of biologics which had DNA sequences completely identical to the human gene (e.g. erythropoietin) but demonstrated immunogenicity, whilst minimal immunogenic responses were reported for other biologics that had structural variations (e.g. IFN- $\alpha$ 2A) (Schellekens 2002). Thus regulatory authorities governing biosimilars still require intensive post-approval pharmacovigilance programs to monitor any differences in safety compared to the original biologic. It is interesting to note that Hirsch (2013) suggests that these current reporting and analysis mechanisms for biosimilars are not sufficiently effective and that more cost-effective pharmacovigilance programs are only recently beginning to develop. Nonetheless, only long-term experience with

biosimilars, well-defined guidelines and advancements in analysis systems will gradually earn the trust of clinicians and patients.

Table 1: Patent protection in major biosimilar markets for the original biologic in terms of exclusivity periods for market access and use of any original biologic data for biosimilar applications (Konski 2011)

Region	Market (years)	Data (years)
EU	10	8
USA	12	4
China	5	6
India	N/A	N/A

### Conclusions

Biosimilars are expected to rapidly increase market share and economic relevance as more biologics reach patent expiry. This is reflected in recent activity relating to international regulatory legislation of biosimilars. Global and regional harmonisation of these guidelines is crucial for encouraging significant investment by biosimilar manufacturers. Nonetheless, these guidelines will evolve as new data and analysis technologies come into play. Safety data and experience with biosimilars with time are essential for regulatory agency, clinician and patient confidence. Despite various challenges, biosimilars will flourish in the near future due to the increasing financial burden on global healthcare systems.

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