Biosimilars: Experience to Date and the Potential to Improve Access for Patients in the United States

Introduction
Biologics are truly innovative therapies, but they are extremely expensive. The development of biosimilar medicines is an emerging field that is generating high levels of interest within industry, and offers the prospect of increasing patient access to these highly effective medicines. Currently, the global biosimilars market includes monoclonal antibody (mAb) biosimilars for the treatment of cancer and autoimmune conditions (e.g., rheumatoid arthritis), as well as insulins, interferons, erythropoietin, filgrastim, somatropin and follicle stimulating hormone. Of these, the mAb and insulin markets are forecast to record the highest growth rates, with these two segments representing a projected 46% of the global biosimilars market by 2018, by which time many leading brands will have lost their patents. As a result of these pending patent expiries, the biosimilar clinical trial industry is booming. Reports vary, but the number of biosimilar candidates in the global pipeline appears to be around 900; however, only 305 are in clinical trials. The time and financial investment needed to develop and market a biosimilar is high, taking seven to eight years and costing between $100 million and $250 million.

Background: Challenges to Biosimilar Development
Companies wishing to develop biosimilars face a variety of challenges, including:

- The reluctance of some investigators to become involved in biosimilar trials, possibly in deference to the manufacturers of new chemical entities (NCEs) and innovative products.
- Lack of knowledge among investigators of biosimilars, with some taking a “wait and see” approach due to the potential for untoward safety events. Some reports cite that as many as 40% of United States (US) investigators lack knowledge about biosimilar development, and this is not surprising as other reports cite 20-30% lack of investigator awareness in the European Union (EU), where biosimilars have been on the market for over eight years.
- Insufficient education around financial benefit to patients in biosimilar trials.
- Some investigators are not aware that there is the potential for commercial price discounts of 10-50% when compared with reference product prices.
- The fact that regulatory pathways are still evolving in some markets.
- Difficulty in copying biosimilars (they are challenging to make).
- Lack of chemistry, manufacturing and control (CMC) expertise.
- The high level of investment required for biosimilar clinical trials.
- The risk that the clinical trial may fail to demonstrate comparability.
- Strong competition in this sector.
- Need for capital to defend potential intellectual property-related cases.
- Life cycle plays by originators to gain patent extension or additional regulatory exclusivity.
- The fact that lobbying groups for originator companies in the US are well funded and active.

This paper focuses on the patient’s ability to access the originator biologic, including the financial burden on patients of obtaining the originator biologic and the financial burden on the US economy. Discussions consider how development of biosimilars may alleviate this situation. The advantages to patients and physicians who participate in the clinical development of biosimilars are also described. Unless otherwise noted, all costs are cited in US dollars.

Biosimilars Could Significantly Reduce Healthcare Costs
Present expenditures on healthcare in the US account for 20% of GDP. The cost of biologics contributes significantly to this situation and these products are part of the battle to control healthcare costs; the US spent some $80 billion on biologics in 2013. Biologics are, on average, 20 times more expensive than small-molecule chemical drugs, and their percentage of the pharmaceutical market is expanding. It is estimated that 46% of the world biologic market in 2010 was in the US, where, unlike the EU, prices are not regulated. The introduction of biosimilars in the US can be expected to have a significant impact on healthcare costs. Presently, there are no biosimilars approved via the 351(k) pathway (established in 2010 as the regulatory pathway to approve biosimilars) in the US, and so we have to look to EU data to understand their potential financial impact.

In the EU, biosimilars are, on average, 30% less expensive than the branded originator products. One study estimated that biosimilars will have saved between 11.8 and 33.4 billion Euros in eight EU countries between 2007 and 2020. While these savings in the EU are highly significant, the effect in the US may be even greater. It has been estimated that the potential savings in the US from just 11 biosimilars in the time period of 2014 to 2024 would be $250 billion.

The Financial Impact of Serious Illness to Patients in the US
To manage the impact on their own budgets, US healthcare payers may exclude coverage of biologics...
from insurance plans, or have increased restrictions (see Figure 1). These may include step therapies and prior authorisations, utilisation reviews, retrospective claims reviews, and refusal to reimburse off-label use. All these elements can impact patient access to therapies, and require patients to assume significant cost burdens. Payers are also sharing costs by moving biologics from the medical to pharmacy benefit, which require deductibles and co-insurance, again increasing higher premiums on patients. Higher premiums for employers are passed onto employees, again increasing the cost burden on patients. For example, the average copayment for oncology biologics is $44, and the average co-insurance is 22%. For a drug that costs $60k per year, this is a significant cost that the patient pays out of pocket.17, 18, 19

Escalating healthcare costs have resulted in a dramatic increase in the number of patients declaring bankruptcy in the US. A study conducted in 1981 demonstrated that only eight per cent of families filing for bankruptcy did so as a result of serious illness.20 By 2001, almost 50% of people declaring bankruptcy cited serious illness as the cause of their financial collapse,21 and by 2008, this number had risen to 61%. At that time, 92% of those declaring bankruptcy had medical debts greater than 10% of their pretax family income. Most were well-educated, owned homes, and had middle-class occupations. In 2007, before the most recent economic downturn, an American family filed for bankruptcy in the aftermath of illness every 90 seconds, three-quarters of whom possessed medical insurance. Many families found themselves under-insured, and responsible for thousands of dollars in out-of-pocket costs. Others lost their private insurance when they became too sick to work. A quarter of employers were found to have cancelled coverage immediately when an employee suffered a disabling illness, and another quarter did so within a year of diagnosis. All of these financial pressures are driving the need for more cost-effective options for patients – both in developed and developing markets (see Figure 2).

Use of Biosimilars
As of April 2014, biosimilars have been on the market for eight years and around 300 million patient days have been generated, according to Paul Greenland of Hospira, chair of the European Generic Medicines Association (EGA) European Biosimilars Group (EBG) Biosimilars Market Access (EBG-MAG).23 Biosimilars are being used in the EU, Canada, Japan, and Australia, and have the potential to improve health outcomes while minimising costs to patients and global healthcare systems.24

An interesting case example of how biosimilars can improve access to care is that involving granulocyte-colony stimulating factor (GCSF). GCSF is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and releases them into the bloodstream. Functionally, it is a cytokine and hormone and is produced by a number of different tissues. One pharmaceutical analog of naturally occurring GCSF is filgrastim. In several markets, GCSF usage had either been declining (as in the case of the United Kingdom), or stabilising (Germany and France) prior to the introduction of the biosimilar GCSF (see Figure 3). Once the biosimilar was launched, however, all three countries saw usage rates rise quite significantly, and in the UK, GCSF regained its place as first-line therapy due to the lower cost of biosimilars.

The Benefits to Patients of Enrolling in Biosimilar Clinical Trials
Many large scale Phase III trials involving potential biosimilar products are being started in the US, and are listed on www.ClinicalTrials.gov. This creates a unique opportunity for both patients and treating physicians. Unlike Phase III trials for novel therapies where the
patient may be randomised to receive placebo, biosimilar Phase III trials do not require use of placebo. Participants are guaranteed to receive active therapy, the approved originator or a copy of the originator product. Before such Phase III trials can begin, the FDA requires the biosimilar developer to have completed extensive laboratory work to ensure the biosimilar is indeed a very close copy of the branded product. In addition, pharmacokinetic equivalence between the branded product and the copy must have been established, usually in healthy volunteer studies.

Of potentially great interest to patients considering biosimilar and other clinical trials is the fact that the sponsors generally pay the entire cost of treatment during the trial. In addition, sponsors may also offer an extended access programme that allows the patient to continue receiving free supplies of the product after the trial has ended. The benefits to those without insurance are obvious.

The Benefits to Physicians of Participating in Biosimilar Clinical Trials

Similarly, by participating in biosimilar trials, treating physicians can provide biologic products to their patients without the need to negotiate with insurance companies. Physicians can also be assured that their patients will not have to refuse or discontinue treatment due to costs alone. Physicians also have the opportunity to gain experience with biosimilars before approval. The experience gained during the conduct of a biosimilar trial may potentially influence formulary decisions and help inform other physicians as these products are commercialised. Biosimilars appear to be a logical consequence of patent expiration and investigators can benefit their patients through their involvement.

Summary

- The rising cost of biologic products has placed a significant burden on the US economy. Biosimilars have the potential to significantly reduce this burden as demonstrated by their use in Europe over the past eight years.
- Even for patients with insurance, high co-pays and co-insurance on biologics may place a significant financial burden on their families.
- Participating in clinical development programmes for biosimilars can significantly reduce the financial burden on patients not just for their medications, but for their overall healthcare costs as well.
- Physicians offering their patients access to biosimilar drug development programmes can offer biologic treatments without the need for insurance company approval and be sure that patients will not have to refuse or discontinue treatment early while enrolled in the study.
- Participation in biosimilar trials provides physicians with opportunities to position themselves within a growing industry.

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