CURRENT TRENDS OF BIOSIMILAR GROWTH OPENS OPPORTUNITIES FOR BANGLADESH

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ABSTRACT

Many blockbuster biologics worth US$ 50 billion will lose patent protection over the next few years in US alone. Since the top 25 biologics are driving 83% of global sales, patent expiry of many of these products is opening up new possibilities for biosimilar players in the next five years. Shifting in disease patterns, product demand, and better tertiary care boost enormous commercial opportunity for the companies interested in biosimilars. However, due to the high clinical development and manufacturing costs, the price difference between biosimilars and corresponding originator products is still a challenge. It needs at least 40-50% price reduction from branded products to meet customer's expectation. Being a new field based on a new regulatory pathway, biosimilars are in direct competition with some very large, well-established innovator companies with enormous budgets. Moreover, the development of second-generation biopharmaceutical products in the market perhaps with improved safety and efficacy than original first-generation products is again a challenge for biosimilar marketing. But in the case of Bangladesh which meets her 97% of pharmaceutical local market demand, biosimilar production will significantly reduce the dependency on imports of the expensive biotherapeutics. For instance, India is attracting large investments in biosimilar research, clinical trials and manufacturing and is expected to grab at least 20-25% of global biosimilar market share because of its established infrastructure, talent pool, and consistent quality compliance within the next five years. Similarly, Bangladesh can enjoy facility and development costs than peers in developed countries and add another pillar of success achieved in small molecule generics by partnering with large multinational corporations for clinical trials and regulatory approval process in EU/US. Incepta Pharmaceuticals Ltd

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has developed the country's first GMP compliant research-cum-commercial integrated facility to synthesize biosimilars like filgrastim, interferon, erythropoietin, and few more products using recombinant DNA technology.

Key Words: Biosimilars, Innovator, Incepta, Recombinant DNA technology.

INTRODUCTION

Unlike generic small molecule drugs, biosimilars or follow-on biologics (FOBs) are not chemically identical to the original product. This is because of proteins are large, complex molecules with innate variability which cannot be completely controlled during manufacturing process. Consequently, biosimilar manufacturers must go to great lengths of demonstration that their products have sufficient likeness to the originator molecules both chemically and structurally. However, the challenges associated with high cost, long incubation time and technical precision, development of FOBs have recently been made easier to demonstrate that biosimilars are similar to originator molecules due to cutting edge analytical advances and effective validated methods of bioassays.

Discussions about biosimilars began (late 1990s) with patent expiry events of several blockbusters biopharmaceutical drugs which were imminent. In 1984 it was realized that the Hatch-Waxman Act or Drug Price Competition and Patent Term Restoration Act [1,2], the legislation that guides the development and commercialization of generic versions of small molecule drugs, did not provide a legal regulatory framework for the approval of biosimilars in the US. Likewise, there was no regulatory guidance or precedent for approval of this class of molecules in Europe or anywhere else in the world. This marked the beginning of a long and often vituperative debate about whether or not biosimilars ought to be made commercially available. Not surprisingly, innovators with approved biopharmaceutical products already on the market steadfastly opposed any legislation for biosimilars whereas small molecule generic manufacturers were in favor of it. Finally, in 2005, the European Medicines Agency (EMEA) crafted regulatory guidance that allowed for marketing approval of biosimilars in the European Union (EU). Since January 2006, EMEA has granted marketing authorization for 18 new biosimilar products [3] marking the beginning of a new era in the biopharmaceutical industry.

While the EU and other countries (Australia, Japan and Canada) allow for approval and commercialization of biosimilars, there is still no straight way of legal, regulatory framework for approval of FOBs in the US. Until recently, American innovator companies and their allies refused to consider any legislation that would allow approval of FOBs in the US. However, the commercial availability of biosimilars in Europe, Asia and South America coupled with the looming specter of US healthcare reform, forced American innovator companies to recognize that FOBs were inevitable and will eventually be sold in the US. To that end, there are two pieces of biosimilar legislation presently being considered by the US Congress [1,2]. Both bills allow for US regulatory approval of FOBs, but differ in the length of the so-called data exclusivity period, a specified period of time that the US Food and Drug Administration (FDA) cannot rely on innovator data to approve FOBs and whether or not FOBs, like small molecule generics, are interchangeable with or can be substituted for prescription innovator products. Innovator companies are lobbying for 12 years of data exclusivity (from the date that the innovator product was originally approved) and vehemently oppose any provisions for interchangeability or drug substitution. In marked contrast, FOB manufacturers favor five years of data exclusivity (which is identical to the data exclusivity period for generic small molecule drugs) and language that would allow FDA to determine whether interchangeability or substitution may be appropriate for some FOBs.

Bruce F. Mackler, PhD, JD, a lawyer who specializes in FDA regulatory matters, contends that "the 12 year data exclusivity period for FOBs is the 800 lb gorilla in the room" and may be slowing down congressional action on biosimilar legislation [2]. While US market is a large portion of global biologics sell, non-regulatory including EU markets has priority to biosimilars when offered at significant price difference. The obligation of similarity for biological molecules is a constant fact compared to small molecules. But how the effect of similarity on the function of biological molecule is unexplained until recently the technology priority benchmark is established in molecular biology. Bangladesh in follow up of its strong position in small molecule pharmaceuticals should formulate biosimilar guideline in the light of EU and WHO regulations and go forward to offer biosimilars at affordable price over biologics. China and India have already established very successful stories in biosimilars managing huge number of patience in need of treatment by biotherapeutics.

GLOBAL SCENARIO AND HURDLES

The biopharmaceutical market is one of the fastest-growing segments of the life sciences industries, TechNavio's analysts forecast the global biosimilar market to grow at a compound annual growth rate (CAGR) of 27.58% over the period 2013-2018 [(4)]. It is growing four times as fast as the small molecule market, and biopharmaceuticals are expected to represent 30% of all marketed drugs within the next five years. Twelve biological products with global sales of more than US$ 67 billion will be exposed to biosimilar competition by 2020 [(5,6)]. This big market opening coupled with increasing downward pricing trends for biopharmaceuticals and biologics, has created an enormous commercial opportunity for companies interested in developing biosimilars. As the figure 1 shows three chemical blockbusters, Effexor, Lipitor and Plavix, with patent expiration dates of 2010, 2011 and 2012 respectively [(7)]. It is clearly shown in the figure that a decrease in global sales of each aforesaid molecule follows after the year of patent expiration.

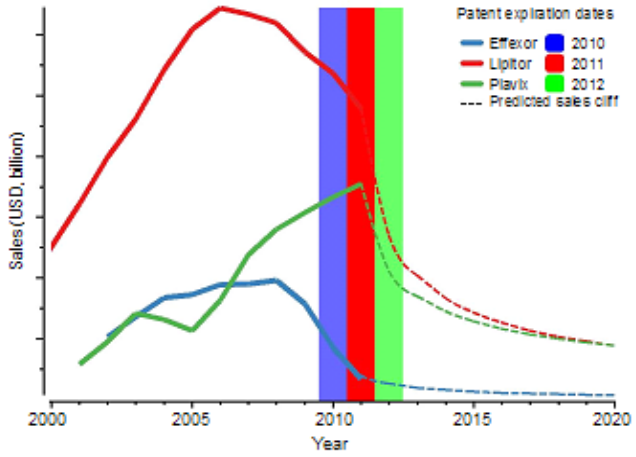

Figure 1

Global sales for three blockbuster chemical drugs: Effexor, Lipitor and Plavix. The solid colored lines represent the annual sales of the product until 2011; the dotted lines represent a projection of the sales for the following years based on Effexor's drop in revenue drop. The shadowed areas correspond to the patent expiration year as indicated

in the legend of the figure [9].

On the other hand, out of biologics sales (US$ 142 billion in 2011) which are equivalent to 19% of the global biopharmaceutical market in terms of revenue [7], more than a third of this value (37.6%) is captured by the top ten selling biologic products. The size of the market and its evolution from 2004 to 2011 is shown in figure 2, highlighting the top ten selling brands: Humira, Enbrel, Remicade, Rituxan, Avastin, Lantus, Herceptin, NovoLog, Neulasta and Lucentis. Big share of biologics market presents huge possibility of biosimilars to replace biologics at the expiry of patent protection.

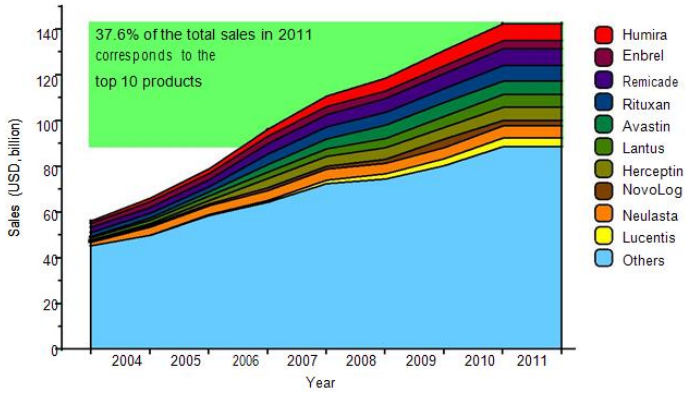

Figure 2

Evolution of global sales for the top ten branded biologic drugs from 2004 to 2011. The products below account for 37.6% of the total biologics market value, adding up to US$ 53.4 billion in 2011 [9]).

It is important to note that hurdles related to commercialization must be overcome before this industry can be transformed into a profitable business opportunity. It is known that the costs associated with developing and manufacturing biosimilars will be much higher than those for traditional small-molecule generics. Apart from cost, almost all biosimilar products will require some form of human clinical testing before being granted regulatory approval or marketing authorization. Eventually, development and production costs will be increased. This affects the margins on these products which might be substantially lower than previously anticipated. Biosimilar manufacturers recently estimate development costs in the range US$ 40 million to US$ 100 million which however

depends upon the complexity of the biosimilar protein being developed. This scenario supports the fact that large, well-established drug makers with significant financial resources are only capable of introducing products to market. High cost in clinical development and manufacturing especially considering the waiver involved which is less than that of biologics, the price difference between biosimilars and corresponding originator products will likely be less than previously thought. Generally, 50% to 80% price reductions compared to brand were expected for biosimilar molecules [8]. However, over time, it is estimated that 20% to 25% cost savings for biosimilars is more realistic. For example, Sandoz launched Omnitrope, (biosimilar version of human growth hormone (HGH)) in Germany two years ago with the discount of price by 20% as compared with Eli Lilly's Humatrope brand. Also, in Australia biosimilar versions of HGH are sold at a 25% discount as compared with their branded counterparts [8, 1-3]. Another important practical scenario comes in the light despite that 20% to 25% cost savings platform concept for biosimilars may be attractive to insurers and healthcare payers, these discounts could be enough to induce physicians' choice of prescription to switch from innovator brands to biosimilars. Moreover, there are many innovator companies who are prompt in introducing second-generation biopharmaceutical products on the market with better features such as improved safety and efficacy, less frequent dosing schedules, and easily accessible technologies.

Because the United States is the largest biopharmaceutical market in the world, and more than 50% of all biopharmaceuticals are sold in America, the commercialization potential of this new class of molecules is still a challenge. This is the reason why the current biosimilar/FOB market is small compared to small molecule generic market. At the same time, the small size of the market is due to the lack of a U.S. regulatory approval pathway for FOBs. Thus the fact comes to the understanding that the global biosimilar market size will have to face challenge until legislation for approval of these products is enacted in the United States like it has already followed in European Union. The good hope is that the pace of innovation does not mean only for biologics but for biosimilar companies who are using modern technology platform to develop biosimilars at very similar proximity. This is how the confidence on biosimilar drugs is increasing in Europe. Filgrastim is one of the successful FOBs in Europe which replaced growing trend of biologics market. Thus, it is not surprising to realize that the delay of US approval of biosimilars in their market because of inclusion of the 12 year period of data exclusivity will let American biosimilar companies compete very high with foreign biosimilars for U.S. regulatory approval [8,1-3]. Eventually, a good portion of biosimilar market will be enjoyed by the early entrants. Today's advantageous scenario of US

market for biologics is accumulating hurdles for tomorrow's biosimilar market as a cumulative threat. The parallelism of human need in relation to affordability and expectation on modern technologies is a time bound fact to promote human civilization to grow harmoniously. This is why biosimilar acceptance is increasing in Europe and many other countries in the world without much presence in value in money but value in contribution for mankind.

FUTURE MARKET LEADERS AND PROSPECTS OF BANGLADESH

There are a large number of companies already jockeying for position and competing in this space. These companies range in size from small startups to major generic manufacturers, and most of them are located in Europe and India. In Europe, Biopartners, Hexal, Ratiopharm, Sandoz, Stada, and Teva have emerged as early industry leaders. Other smaller European companies include CT Arzneimittel, Hospira, and Medice. In India, large companies like BioCon, Dr. Reddy's Laboratories, and Ranbaxy have taken the lead — although several smaller companies, including Intas and Zydus Cadila, are also developing biosimilar products. Noticeably absent from the mix have been American big pharmaceutical and biotechnology companies. However, this has begun to change with drug makers AstraZeneca and Eli Lilly & Company expressing interest in FOBs and the recent launch of Merck BioVentures (MBV).

A look at our neighbor India shows that biotech revolution which continues to expand fast. The Indian biotech industry is one of the fastest growing industries in the world. According to a recent report prepared by the Association of the Biotech Led Enterprise (ABLE) for the Department of Biotechnology (DBT), in the period of 2000-2011, revenue from the biotech sector was phenomenal US$ 3 billion and is expected to reach US$ 10 billion in 2015. Of the 350 biotechnology companies in India, 175 are based in South India [(9).] .The Indian Biospace is dotted with a growing number of multinationals like Eli Lilly, Novo Nordisk, AstraZeneca, Baxter and Roche.

Unlike India, Bangladesh has yet to develop a significant biotechnology industry and capitalize on a fast growing global industry of US$ 100 billion. Agriculture and pharmaceuticals are key sectors in Bangladesh. Many of the next generation of medicines (e.g. antibiotics, antibodies, hormones and vaccines) will be biotechnology derived.

Bangladesh is at an early stage of biotech development although pharmaceuticals are the most promising industrial sector. There are 257 pharmaceuticals companies registered and among them 197 are operational. Annual 2011 sales

was 8,048 crore taka (US$ 1.06 billion) with a growth rate of 24.63%. The industry is providing employment for about 1,00,000 skilled personnel. Bangladesh among all the least developed countries (LDCs) has highest pharmaceutical industries. Primarily generic industries are producing about 8000 different brands which met 97% of the domestic demand. Local companies enjoy 86% market share. Of the 257 registered pharmaceuticals, the top 10 players account for 65% market share [10,11] .

Bangladesh can penetrate into regulated and unregulated markets since many companies have acquired international certifications like UK Medicines and Healthcare Products Regulatory Agency (MHRA). Technological excellence has always been the highlight of the pharmaceutical industry. Export of pharmaceutical finished product is evolving. This industry contributed US$ 52.65 million in 2011 by exporting to 83 countries as well as manufacturing 97% of country's requirement of medicine and only 3% is imported which are mainly biopharmaceuticals. Twenty one local pharmaceuticals companies are producing 41 APIs currently. However 80% of the APIs are imported. Neighboring countries like Pakistan meets 90% and Srilanka meets 98% of its bulk drug requirements through imports [12].

Bangladesh can enjoy facility and development costs than peers in developed countries and add another pillar of success achieved in small molecule generics by partnering with large multinational corporations for clinical trials and regulatory approval process in EU/US. Due to the crying need of biotech products for the achievement of self-sufficiency for human medicines, the pharmaceutical companies of Bangladesh are turning to biotech products gradually. Several companies have already introduced anti-cancer, anti-HIV/AIDS drugs, human insulin, and many other companies are planning to launch biotech products to keep pace with the world's pharmaceuticals market trend, to fulfill the local demand of biotech products, as well as to export those products to other countries.

Incepta Pharmaceuticals Ltd. has developed the country's first GMP compliant research-cum-commercial integrated facility to synthesize biosimilars using recombinant DNA technology. The pilot facility currently simulates the potential process for production of insulin, filgrastim, interferon, erythropoietin, etc, in pilot scale, which will be followed by dosage form design and commercialization of biosimilars. There are a growing number of players in the biosimilar/FOB market but better capitalized companies invest early based on their future plan to ultimately dominate the market. The fact of biologics presence in the global market is context dependent whereas biosimilar

market growth is a function of health care need. How similar is similar a biosimilar is a solved equation for today's molecular biologists working with better concept at better technology platform.

DISCUSSION

The debate lasted for a decade gave the shape biosimilars/FOBs finally a reality. The last hurdle to be overcome before the full commercial potential of these products can be realized is legislation that allows approval of FOBs in the United States. The number of applications for FOB registration in US market will be beyond expectation once U.S. biosimilar legislation is enacted and this trend may overwhelm the FDA and unwittingly slow approval of some biosimilars [8]. Many pharmaceutical companies will then announce their intention to get into the biosimilar market which will affect the monopoly price advantage of biologics. The trend that is followed for shaping up biosimilar/FOB market will result in extremely competitive situation and the barriers to entry might be more affordable than previously anticipated by some biosimilar/FOB manufacturers. Although innovator companies are alarmingly active to employ all available means and tactics to protect their multibillion dollar biopharmaceutical franchises from generic encroachment, the conceptual changes happening continuously in science is ultimately affecting positively regulatory requirements to change for Biological drugs at accelerated rate. Small molecule pharmaceutical manufacturing companies will also make their inroad into large molecule biosimilar business. Finally, despite the entry in good number, the companies that are likely to emerge as dominant players' in the biosimilar/FOB marketplace are larger in their strength indicating that the more sophisticated manufacturers world class infrastructures and financial resources will no doubt compete with innovator companies.

CONCLUSION

The hope for the biosimilar companies is increasing as because of emerging technological support and research outlook that are becoming available for researchers. The difference between biosimilar and biologics researches is nothing from technology but mostly the way a biologic company experiences a molecule of its group such as diabetic regiments of Novo Nordisk. Whereas compared to biologics research, biosimilar researchers are more focused to technology and process development which is not far from generating idea of new molecule using reverse engineering. Providing that resources are there in biosimilar companies, any research using biologics as templates is possible to develop following innovative approaches. Bangladesh as a late entrant in biosimilar research has ample opportunities to grow in regulatory and non regulatory markets. When competition is always a relative term in this

open information world, Bangladesh can capitalize modern technology platform available in contemporary time, its relatively low cost white collar expertise, cost effective investment, in flow of multidisciplinary graduates from different universities and good success in regulatory framework in pharmaceutical (small molecules) business.

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