Biosimilars Manufacturing- Cost reduction vitalities

The Biopharmaceutical industry has emancipated a surge of growth over the past 20 years, primarily, due to blockbuster launches of novel biologics and the emergence and acceptance of biosimilars. With an industry value of around $200 million, including four US approved and twenty EU approved products, the biosimilars market is slowly but surely carving a niche for itself in the competitive pharma-biopharma market [1]. The graph below depicts of the 15 of the globally highest selling products in 2017, 10 are biologics [2]. The top 15 products' sales for 2017 are approximately 112 billion USD, of which 87 billion USD was contributed by the sale of biological products alone.

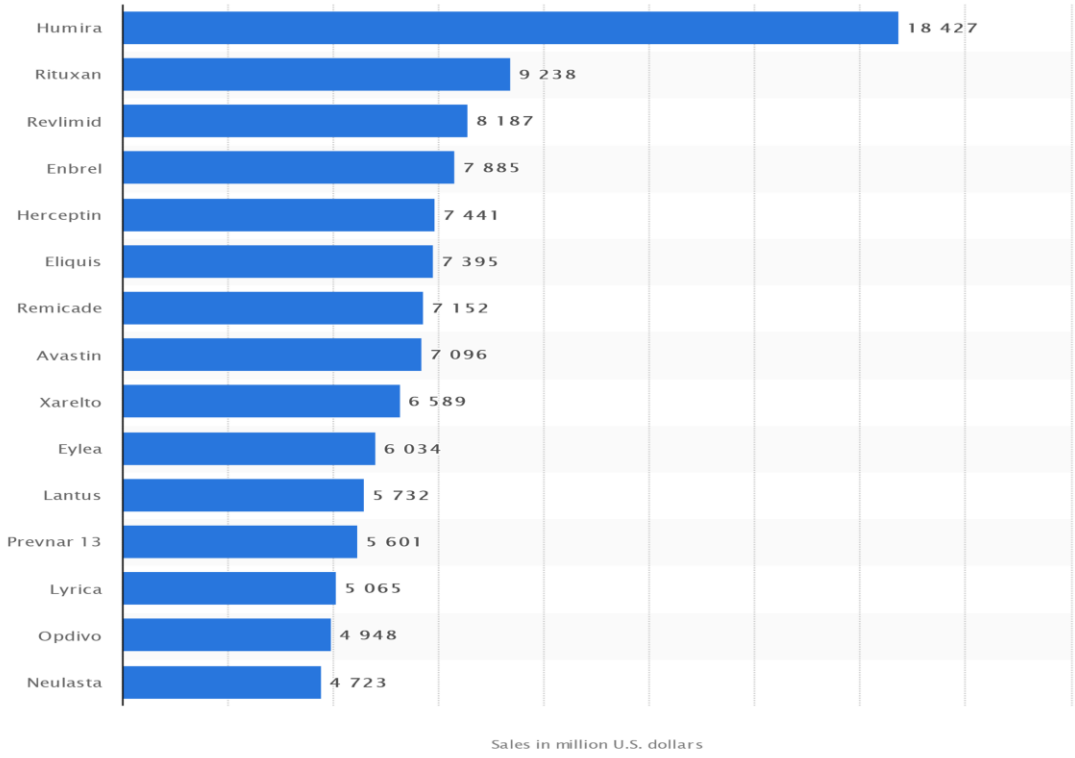

Figure 1: Market trends of Biologics sales for the year 2017

Biosimilars certainly offer cost-saving approaches to the patients over the innovator molecules. Over the past ten years, the EU has established a much clearer pathway for accepting biosimilars when compared to the US, which is still evaluating a suitable regulatory pathway and establishing guidance for interchangeability.

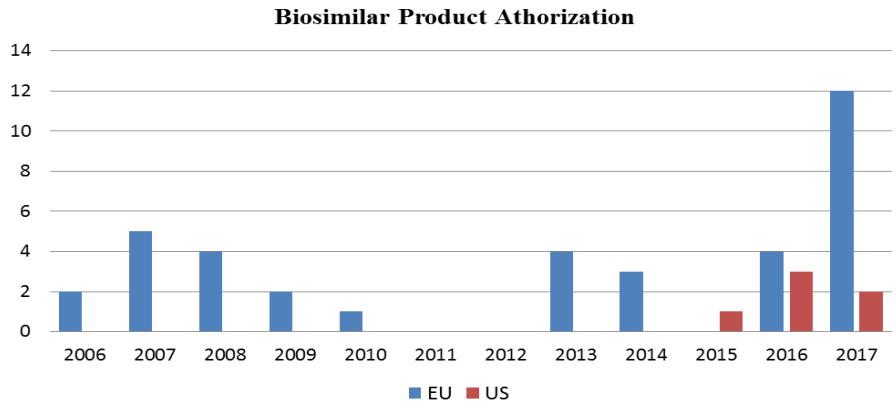

Figure 2: Biosimilar product frontier in the US with respect to EU

The graph above stealthily depicts how the biosimilars frontier approved by EMA is emerging at a fast pace in the EU [4]. Lags in the US are probably because, unlike the EU, the US did not implement a regulatory framework for biosimilars evaluation until after enactment of the Biologics Price Competition and Innovation (BPCI) Act of 2009. Given that the first US biosimilars drug was approved almost a decade after the first in the EU, the number of authorized biosimilars drugs in the EU far exceeds that of those approved in the US. With the staggering increase in drug prices and additional pressure by the Trump administration, the FDA has been placed in the spotlight. Subsequently, the organization's new commissioner, Dr. Scott Gottlieb, has been actively advocating for a change and reduction in drug pricing [4]. All these factors have hence led to an ever-mounting pressure on the US regulators to slash drug prices, and the US FDA is trying to facilitate a pathway to ensure faster biosimilars approvals and entry to the market.

Owing to the rapid growth of the biotechnology market, the imminent patent expiry on several major biologics, and the establishment of regulatory frameworks; the key driver for the biosimilars market, cost containment pressures could be relived! A prominent example would be that of Inflectra (infliximab), which the FDA had approved in 2016. According to reports, Merck's list price for its newly launched biosimilar Renflexis (infliximab-abda) represented a 35% discount to originator biologic Remicade and undercuts a competing biosimilar by 20%. Renflexis was to be introduced in the US with a wholesale acquisition cost (WAC) of $753.39. So this would imply that a 100-mg dose of Remicade (infliximab, Janssen) had a WAC of $1,167.82, while Inflectra (infliximab-dyyb, Celltrion/Pfizer) had a WAC of $946.28 [5]. In another instance, for an older product – Filgrastim- the cost reduction of the biosimilars is even more significant up to 50% to 60% discount to the originators' sale price before the launch of

the biosimilar. According to retrospective research carried out by a team of Italian researchers, the cost of one vial of Tevagrastim at the Guglielmo da Saliceto Hospital was Euros 34.10 (US$42.51), while one vial of Zarzio cost Euros 10.85 (US$13.5). This was 56% and 86% cheaper, respectively than one vial of Neupogen, which cost (Euros 77.53/US$96.65). It has also been estimated that biosimilars could cut spending on biologicals in the US by US$44 billion over the next decade [6].

Price pressure on biosimilars has driven the Biopharma industry to more economical measures such as cost-effective manufacturing processes, single-use technologies, and outsourcing trends, throughout the biopharmaceutical industry.

One of the common counter-intuitive trends is downsizing or right-sizing the entire process to increase production. Traditional manufacturing processes for biologics make use of large, fed-batch reactors and oversized chromatography columns that end up wasting time or material 3. Lowest costs are generally associated with the very large scale stainless-steel manufacturing. Most of the biosimilars products in the market are of high value and low volumes where in, increasing the manufacturing capacity (to reduce the costs) only causes a significant increase in the output whereas there is an inadequate market uptake for the same. Upstream process scale-up can make use of perfusion reactors, which use a constant supply of cell-culture media while removing unwanted byproducts throughout a prolonged production run of typically more than 20 days. Downstream processing goals include multiple stages of purification and concentration. Disposable, single-use filtration is an alternative to outdated centrifugation methods that are difficult to scale and complicated to use. Expanded-bed absorption (EBA) offers an alternative to oversized chromatography columns. EBA combines filtration, centrifugation, and chromatographic separation into a single step and can handle high-density cell feeds directly from the bioreactor 3. Nanofiber adsorbents are another resin column alternative. They are able to flow at fast rates, albeit with low binding capacity. Taken together, upstream and downstream process innovations can be packaged into an automated, continuous, small-footprint antibody production facility that can fit into a single cabinet in approximately 20 square feet of a GMP production facility. In a concept described by Jacquemart et al [7]., one cycle of downstream processing was completed in 24 hours [3].

Another alternative would be the use of Single-use manufacturing equipment. This, if done right, can be very competitive, such as attaining costs below $200/gram, along with the inherent

flexibility, lower capital expenses, faster turnaround, smaller footprint and other benefits of single-use bioprocessing

Of all the proposed solutions, one of the remarkably known would be outsourcing to emerging markets, in emerging economies, such as India and China. According to reports, costs of manufacturing were quoted as likely to have the lowest costs averaging around $160/gram [1]. Owing to the advanced technology, competency and lower man power costs that these countries have, outsourcing to emerging markets vouches to be the best means to cost reduction.

Cost competition is transforming the biopharmaceutical market with biosimilar manufacturers leading the way. Going forward, the biosimilars manufacturing would thrive into the emerging economies such as India because of budding cost-effective CMOS and Biopharmaceutical manufacturing companies.

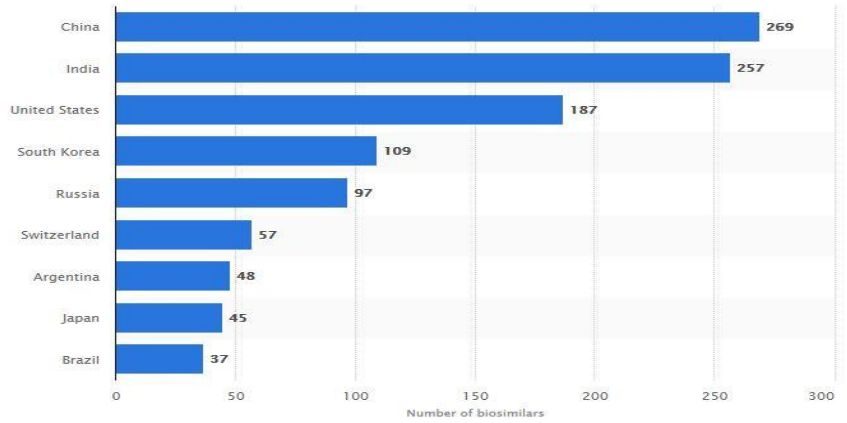

Figure 3: Market trends across regions for Biosimilars sale for the year 2017

As seen in the above graph, India and China put together accounted for over 500 various Biosimilars in development as seen in the graph above. This could be primarily attributed to the lower manufacturing costs in these countries as well as the adoption of smaller equipment, continuous processes, and single-use technologies that are replacing large-scale reactors. The competition will increase, and attaining low costs, generally involving using current vs. older legacy bioprocessing technologies, is critically needed by biosimilars manufacturers to support discounts and defend against the considerable expected biosimilars competition. The ultimate beneficiary will be patients, who are likely to see reductions in the currently astronomical price of life-saving biologic therapies [3].

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