



# Biological Drugs

Challenges to Access

Amit Sengupta

TWN

Third World Network

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**TWN**  
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## Chapter One

# The Growing Therapeutic and Commercial Importance of Biologics

BIOLOGICAL drugs (commonly referred to as ‘biologics’ or ‘biopharmaceuticals’) are drugs produced through biological processes. They currently target diseases which, hitherto, had very limited or no available treatment options – including several types of cancers, autoimmune diseases and other non-communicable diseases. These drugs are different because they are produced in living cells. Biologics are larger in size and more complex than the ‘small molecule drugs’ (SMDs) manufactured using chemical synthesis processes. Biologics have several potential advantages as they can, theoretically, be tailored to hit specific ‘targets’ in the human body.

The global list of top-selling drugs is increasingly populated by biologics (see Table 1). Revenues being generated by biological drugs are huge: the projected global sales of the top-selling biologic, AbbVie’s Humira (adalimumab) – a drug used to treat autoimmune disorders such as rheumatoid arthritis – in 2018 are US\$20 billion, equal to about two-thirds of the entire pharmaceutical market in India in 2017.

The penetration of biological drugs in standard treatment practices is still comparatively lower than SMDs, due to their high costs, treatments being currently available for only a limited number of diseases and the need for a developed health system to supervise treatment with biologics. However, in some therapeutic areas treatment with biologics is already quite significant, especially in high-income countries. An estimated 19% of rheumatoid arthritis (the disease area where use of biologics has been the

highest) patients in Europe were accessing biologics in 2010.<sup>1</sup> In 2014, there were 3.1 million patients in the US being treated with one of seven top-selling biologics available in the country.<sup>2</sup> In 2015, the World Health Organization (WHO) included two new biological drugs for cancer treatment, trastuzumab and rituximab, in its list of Essential Medicines.<sup>3</sup> The list already contained two older biologics – pegylated interferon alfa (2a or 2b) and filgrastim.

The fastest-growing segment of the market for biological drugs – the recombinant glycosylated proteins segment – is projected to grow annually at 25% by 2018. Within this, the monoclonal antibody segment alone will have an estimated compounded annual growth rate of 41.9% from 2013 to 2018. The US market is clearly driving the growth of biologics – between 2013 and 2014, spending on specialty drugs, including biologics, increased by 32.4%, while spending on SMDs increased by just 6.8%. Sales in the US account for over half of revenues generated by the sale of biologics.<sup>4</sup> By 2016, eight of the 10 top-selling drugs in the US market were biologics.<sup>5</sup>

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<sup>1</sup> Laires, Pedro A et al. (2013) Patient's Access to Healthcare and Treatment in Rheumatoid Arthritis: The Views of Stakeholders in Portugal. *BMC Musculoskeletal Disorders* 14 (2013): 279, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3849024/>

<sup>2</sup> The Biosimilars Council (2017) Biosimilars in the United States: Providing More Patients Greater Access to Lifesaving Medicines. Available at: <http://biosimilarscouncil.org/wp-content/uploads/2017/09/Biosimilars-Council-Patient-Access-Study-090917.pdf>

<sup>3</sup> Malik, Monica et al. (2016) Biosimilars in Low- and Middle-Income Markets: A Case Study of India and Russia. 26 May 2016, <https://am.asco.org/biosimilars-low-and-middle-income-markets-case-study-india-and-russia>

<sup>4</sup> \_\_\_\_\_ (2013) Generating value in generics: Finding the next five years of growth. McKinsey and Company, May 2013, <http://www.mckinsey.com>

<sup>5</sup> \_\_\_\_\_ (2016) The economic impact of biosimilars in the US. 29 July 2016, <http://www.gabionline.net/Biosimilars/Research/The-economic-impact-of-biosimilars-in-the-US>

The anticipated percentage growth rate of biologic and biosimilar markets far exceeds that of the more established SMD markets. The biologics market is set to increase its total market share from 16.6% in 2015 to 22.2% in 2021.<sup>6</sup>

The growing commercial importance of biological drugs is also evident from the rise in patenting activity related to these drugs. In 2009, biological drugs accounted for 60% of the patents filed by the top 10 pharmaceutical companies.<sup>7</sup> Abbott had as much as 80% of the patent filings between 2007 and 2009 focused on biologics.<sup>8</sup> Recent interest in biological drugs is also driven by the fact that several top-selling biologics have gone or will go off-patent between 2013 and 2018. These include blockbusters such as Rituxan/MabThera, Remicade, Herceptin, Humira, Avastin, Synagis, Erbitux and Lucentis.

While many of the discoveries of new biological drugs continue to originate in specialized biotech companies, the drugs are increasingly being developed by leading multinational pharmaceutical companies (hereafter referred to as 'Big Pharma') which had traditionally concentrated on development of SMDs. In recent years many traditional pharmaceutical companies have entered the market for biological drugs, often through acquisitions of smaller biotech companies. Currently biologics contribute significantly to the revenues of Big Pharma. They accounted for 22% of the Big Pharma companies' sales in 2013, and this is projected to rise to 32%

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<sup>6</sup> Results Healthcare (2017) Pharma & Biotech 2017, Review of outsourced manufacturing. [http://resultshealthcare.com/wp-content/uploads/2017/01/Results-Healthcare\\_Pharma-Biotech-2017-Review-of-outsourced-manufacturing\\_Whitepaper.pdf](http://resultshealthcare.com/wp-content/uploads/2017/01/Results-Healthcare_Pharma-Biotech-2017-Review-of-outsourced-manufacturing_Whitepaper.pdf)

<sup>7</sup> Jack, A (2012) Fall in number of patents filed by big pharma. *Financial Times*, 18 March 2012, <https://www.ft.com/content/0912c0ea-70f9-11e1-a7f1-00144feab49a>

<sup>8</sup> Philippidis, Alex (2012) Higher percentage of large molecules compared to small molecules makes it to market. *Genetic Intelligence and Biotechnology News*, 9 April 2012, <http://www.genengnews.com/keywordsandtools/print/3/26751/>

**Table 1: Top 10 best-selling drugs in 2015 and the share of biologics<sup>9</sup>**

<b>Drug</b>	<b>Company</b>	<b>Ingredient</b>	<b>Indication</b>	<b>Biologic</b>	<b>2015 sales (million US\$)</b>
Humira	AbbVie	Adalimumab	Autoimmune disorders	YES	14,012
Harvoni	Gilead	Ledipasvir + sofosbuvir	Hepatitis C	NO	13,864
Rituxan	Roche	Rituximab	Non-Hodgkin's lymphoma	YES	7,327
Lantus	Sanofi	Insulin glargine	Diabetes	YES	7,088
Avastin	Roche	Bevacizumab	Various cancers	YES	6,951
Herceptin	Roche	Trastuzumab	Breast cancer	YES	6,799
Remicade	Johnson & Johnson	Infliximab	Autoimmune disorders	YES	6,561
Prevnar	Pfizer	<i>Streptococcus pneumoniae</i> vaccine	Vaccine	YES*	6,245
Januvia/ Janumet	Merck	Sitagliptin	Diabetes	NO	6,014
Revlimid	Celgene	Lenalidomide	Multiple myeloma	NO	5,801

\* While vaccine manufacture is through a biological process, it doesn't involve recombinant technology (see below)

by 2023. Some of the leading companies poised to benefit from growing sales of biological drugs include Abbott, Roche, Bristol-Myers Squibb, Merck, Eli Lilly and Sanofi.<sup>10</sup>

<sup>9</sup> \_\_\_\_\_ (2016) FirstWord Lists: The 100 best selling pharmaceutical brands. <https://www.firstwordpharma.com/node/1375342>

<sup>10</sup> \_\_\_\_\_ (2015) Pharmaceuticals: Going large. *The Economist*, <http://www.economist.com/node/21637387/print>

## Chapter Two

# How Biological Drugs Differ from Small Molecule Drugs

BIOLOGICAL products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources – human, animal or microorganism – and may be produced by biotechnology methods and other new technologies.<sup>11</sup>

Biologics can be produced through: a) biological processes that do not involve the creation of a new cell (to produce the product), or b) recombinant technology (see Box 1). The major innovation of the last two decades, leading to renewed interest in the promise of biological products, has been propelled by the development of recombinant technology. It must be remembered, though, that biological drugs had been produced before recombinant technologies became available, including, for example, vaccines and antibiotics such as penicillin. However, in this paper we are limiting our analysis largely to biological drugs developed through recombinant technologies.

Biological drugs differ in many ways from SMDs. Biologics are extremely sensitive to the manufacturing process and the starting material. As the starting material is a living cell in the case of new biological products that

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<sup>11</sup> US Food and Drug Administration (2016) What Are 'Biologics' Questions and Answers. <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm>

use recombinant technology, it is impossible to have exactly similar starting cells. Moreover, very small changes in the manufacturing process can bring about changes in the final product. It is impossible for a company producing a follow-on biological product to completely replicate a large, complicated biomolecule, since it doesn't have access to the specific methods and conditions that the original company had in synthesizing and characterizing the compound.<sup>12</sup> This has implications for the development and manufacture of follow-on products. Here it may be noted, however, that even in the case of the original product, there are variations in the product between batches and even within the same batch. Current analytical methods cannot fully predict the structural properties of a biological drug (called 'characterization') though the body's immune system can detect alterations in products missed by analytical methods. This is however changing rapidly as more sophisticated methods of analysis are developed, and it is possible now to almost fully characterize the large complex molecules of which biologics are composed.

The relative uncertainty about the structural characteristics of biologics has led to a reluctance to refer to follow-on products of biologics – that is, similar biologics manufactured by someone other than the originator company – as generics. The biologics industry has introduced the notion that since it is impossible to manufacture an exact replica, follow-on products should be called biosimilars and not generics or bio-generics. Many see this as a ploy to restrict the use of follow-on products by creating doubts in the minds of regulators and prescribers.

The complexity of the manufacturing process for biologics is several orders of magnitude higher than that for SMDs. Conventional pharmaceutical agents are small-molecule chemicals with a defined molecular weight typically between 100 and 1,000 Da. In contrast, biologics are large, complex and heterogeneous proteins with more variable molecular weights,

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<sup>12</sup> Stembridge, Bob (2015) Unique solutions to biosimilar patenting. <http://ip.thomsonreuters.com/sites/default/files/m/Thomson-Article-TPL.pdf>

commonly ranging from 18,000 to 145,000 Da.<sup>13</sup> Further, biological drugs have high immunogenicity – that is, their ability to produce an immune response in the body is of a much higher order than SMDs. This places limitations on the use of biologics in settings where patients cannot be adequately supervised while on biological medicines. Biological medicines come in the form of injectables, further limiting access to these in resource-poor healthcare systems.

**Table 2: Differences between biologics and small molecule drugs**

<b>Characteristic</b>	<b>Small molecule drugs</b>	<b>Biological drugs</b>
Size of molecule	Small	Large
Drug production	By chemical synthesis	By genetic engineering methods Produced in cell lines
Product characterization	Well characterized	Difficult to characterize the product as they tend to be produced as diverse mixture of molecules which are very slightly different from one another
Purification, contamination possibility	Easy to purify Contamination can be generally avoided, is easily detectable and often removable	Lengthy and complex purification process High possibility of contamination, detection is harder and removal is often impossible
Laboratory analysis	Easily analyzed with routine laboratory tests	Current physico-chemical analytical methods or bioassays cannot detect all product variations
Susceptibility to environmental or process changes	Not affected by environmental changes or any changes in the steps of the production process, hence the product is more important than the process	Highly susceptible to the slightest changes in the environment, cell strains or the manufacturing process, hence it remains the most essential aspect of manufacturing
Immunogenicity	Low immunogenicity	Generally immunogenic

<sup>13</sup> Schellekens, Huub (2009) Biosimilar therapeutics – what do we need to consider?. *NDT Plus* (2009) 2 [Suppl 1]: i27-i36; doi: 10.1093/ndtplus/sfn177

## Chapter Three

# Recombinant Technologies in the Manufacture of Biological Drugs

### **Box 1: What are recombinant technologies?**

Biotechnology involves biological processes that have been manipulated or modified in some way through modern science. A major industrial application of biotechnology is in the development and preparation of biological medicinal products using genetically engineered bacteria, yeast, fungi, cells or even whole animals and plants. Some of these biological medicines were originally extracted from tissues and secretions, often of human origin and in relatively small amounts. With the advent of recombinant DNA technology, the preparation of large amounts of highly purified and characterized materials became possible, including products intentionally modified by pegylation (treatment of a complex biomolecule with polyethylene glycol to stabilize it) or changes in DNA sequences, fundamentally changing the manner in which biological substances like these were produced and standardized.<sup>14</sup>

In the case of drugs developed through recombinant technologies, there were two waves of biologic drug discoveries: recombinant versions of human endogenous molecules (i.e., hormones and enzymes found inside the human body) were developed in the 1980s; and more complex products, such as monoclonal antibodies, in the late 1990s.<sup>15</sup>

<sup>14</sup> World Health Organization (2016) Biotherapeutic Products. <http://www.who.int/biologicals/biotherapeutics/biotherapeutic-products/en/>

<sup>15</sup> Calo-Fernandez, Bruno and Juan Leonardo Martinez-Hurtado (2012) Biosimilars: Company Strategies to Capture Value from the Biologics Market. *Pharmaceuticals* 2012, 5: 1393-1408; doi:10.3390/ph5121393

Recombinant biological products include: a) recombinant non-glycosylated proteins; b) recombinant glycosylated proteins; and c) recombinant peptides. Recombinant non-glycosylated proteins include insulin, granulocyte colony-stimulating factor (G-CSF), interferons and human growth hormone; recombinant glycosylated proteins include erythropoietin, monoclonal antibodies and follitropin; and recombinant peptides include calcitonin and glucagon. Of these, the new generation of drugs for cancer and autoimmune diseases comprises those that are characterized as monoclonal antibodies (the convention for such drugs is to use an International Non-proprietary Name (INN) ending in the three letters ‘mab’).

<b>Table 3: Classification of recombinant biological products<sup>16</sup></b>	
<b>Non-glycosylated proteins</b>	Insulin, interferons, granulocyte colony-stimulating factor (G-CSF), human growth hormone
<b>Peptides</b>	Calcitonin, glucagon
<b>Glycosylated proteins</b>	Erythropoietin, follitropin, monoclonal antibodies

<sup>16</sup> Biosimilars Market Product (2013) <http://www.prnewswire.com/news-releases/biosimilars-market-product-recombinant-non-glycosylated-proteins-insulin-filgrastim-somatropin-glycosylated-monoclonal-antibodies-erythropoietin-peptides-glucagon-calcitonin—application-oncology-blood-disorders-233468431.html>

### **Box 2: What are monoclonal antibodies?**

Monoclonal antibodies, or MAbs, are laboratory-produced antibodies that bind to specific antigens expressed by cells, such as a protein that is present on the surface of cancer cells but is absent from (or expressed at lower levels by) normal cells.

To create MAbs, researchers inject mice with an antigen from human cells. They then harvest the antibody-producing cells from the mice and individually fuse them with a myeloma cell (cancerous B cell) to produce a fusion cell known as a hybridoma. Each hybridoma then divides to produce identical daughter cells or clones – hence the term ‘monoclonal’ – and antibodies secreted by different clones are tested to identify the antibodies that bind most strongly to the antigen. Large quantities of antibodies can be produced by these immortal hybridoma cells. Because mouse antibodies can themselves elicit an immune response in humans, which would reduce their effectiveness, mouse antibodies are often ‘humanized’ by replacing as much of the mouse portion of the antibody as possible with human portions. This is done through genetic engineering.<sup>17</sup>

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<sup>17</sup> NIH National Cancer Institute (nd) Biological Therapies for Cancer. <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet>

## Chapter Four

### **Renewed Interest in Biological Medicines**

THERE is, at present, renewed interest in the biologics market, and as a consequence biotech companies are attracting large amounts of funding. According to a PricewaterhouseCoopers (PwC) and National Venture Capital Association (NVCA) report, over US\$2.1 billion was invested in biotech companies in the US in the second quarter of 2015. Four of the five quarters up till then were among the top record-setting quarters for the past 10 years in magnitude of venture capital funding being made available to biotech companies.

When more capital is channelled into a particular area as compared with historical norms, questions around bubbles and over-funding get raised. The question that may be asked is whether there is a funding and valuation bubble in the biotech sector. The growing pool of capital available today could dissipate quickly if market sentiment turns against the biotech sector.<sup>18</sup>

The question is valid if one scans the history of the promise of the biotech revolution. Delivery on the promise of biotechnology has been slow and previous failures would suggest the need for caution. The last time the biotech industry was able to garner current levels of funding was around 2000, when companies promised, and investors believed, that genomics, particularly after the decoding of the human DNA sequence, would revo-

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<sup>18</sup> Booth, B (2015) The Venture Funding Boom in Biotech: A Few Things It's Not. *Forbes*, 23 July 2015, <http://www.forbes.com/sites/brucebooth/2015/07/23/the-venture-funding-boom-in-biotech-a-few-things-its-not/#4db49959439c>

lutionize drug discovery. However, biotech stock prices eventually collapsed when genomics did not yield the promised bonanza.<sup>19</sup>

The current enthusiasm around biotech drugs needs to be tempered by the knowledge that we are yet to see biological drugs that have truly revolutionized therapy in many areas. Most available therapies utilizing biological drugs are clustered around autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and psoriasis, and around some forms of cancer. In the former case (autoimmune disorders), while treated patients have seen significant improvement in quality of life, the new biologic-based treatments do not target life-threatening diseases of an immediate nature. Cancer therapies available in the form of biologics are yet to provide dramatic results – rather, in most cases they effect an incremental increase in survival rates. In fact, in the recent past, it is small molecule drugs such as imatinib (for chronic myeloid leukaemia) and sofosbuvir (for hepatitis C) that have provided dramatic therapeutic breakthroughs.

An associated issue is that of the cost of biologics, including of follow-on versions (called 'biosimilars' or 'biogenerics'). The US market (and to a certain extent the EU market) is fuelling the growth of the biologics sector, but the ability of even these markets to sustain the growth of such high-cost therapies is uncertain unless new breakthrough drugs become available.

This is not to suggest that the predicted growth of the biologics (and biosimilars) market is a mirage or a funding-induced bubble, but to predicate future projections on a bigger realization of the promise of biotechnology towards promoting better outcomes in a larger range of diseases.

The current optimism around the biotech sector is being driven by two factors. As mentioned above, the fastest-growing segment of the biologics market is the recombinant glycosylated proteins segment – projected to

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<sup>19</sup> Pollack, A (2015) Riding High, Biotech Firms Remain Wary. *New York Times*, 18 January 2015, [http://www.nytimes.com/2015/01/19/technology/riding-high-biotech-firms-remain-wary.html?\\_r=0](http://www.nytimes.com/2015/01/19/technology/riding-high-biotech-firms-remain-wary.html?_r=0)

grow annually at 25% by 2018. One of the drivers of this growth, it is projected, is the investment by drug manufacturers in developing biosimilar versions of monoclonal antibodies (over 50 biosimilars of monoclonal antibodies are in the pipeline). This interest is further strengthened as patents on many top-selling biological drugs have expired or are set to expire soon. Other fast-growing products (other than monoclonal antibodies) include follitropin (to treat infertility) and erythropoietin (especially useful in treating anaemia secondary to chronic kidney failure). Optimism around biological drugs is also being fuelled by the high prices commanded by the top-selling drugs.

Big Pharma was not involved in and did not benefit from the success of innovative biotech companies in the late 1990s, but the pharmaceutical giants have recently acquired some of those successful biotech companies to shore up their capabilities in the biotech sector. The mega-mergers of Pfizer and Wyeth, Roche and Genentech, and Merck and Schering-Plough are examples of recent acquisitions by Big Pharma. However, the rate of introduction of new biologics has slowed from the peaks in the late 1990s. One reason for this deceleration is that innovative biotech companies had patented and developed products saturating the currently available approved indications, and regulatory agencies require new products to show better efficacy than the existing ones.

The slowdown in introduction of new biologics is driving interest in biosimilars. Big Pharma, which missed the bus earlier, is now entering the biosimilars market. This is an attractive option for Big Pharma, given that a number of biologic blockbusters have lost or are soon to lose market exclusivity. Top biotech innovator companies are also entering the biosimilars market. For example, Amgen, the largest biologics manufacturing company globally, signed a deal in July 2016 with Japanese firm Daiichi through which Amgen secured an exclusive agreement to commercialize nine biosimilars in Japan.<sup>20</sup> Earlier in 2016, Amgen had an-

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<sup>20</sup> \_\_\_\_\_ (2016) Amgen and Daiichi Sankyo Announce Agreement to Commercialize Biosimilars in Japan. 13 July 2016, <http://www.amgen.com/media/news-releases/2016/07/amgen-and-daiichi-sankyo-announce-agreement-to-commercialize-biosimilars-in-japan/>

nounced plans to launch in the US its biosimilar version of AbbVie's Humira (adalimumab), the world's biggest blockbuster drug.<sup>21</sup>

Established innovative biotech companies fund their research and development (R&D) operations through the revenues obtained from their biologic blockbusters, the majority of which were patented during the wave of biologic drug discoveries of the late 1990s. The strategic decisions of mega generics companies and Big Pharma to enter the biosimilars market are therefore a real threat to the survival of innovative biotech companies.<sup>22</sup>

Companies such as Teva, Sandoz and Hospira, the largest generics companies, are already commercializing biosimilar hormones, cytokines and enzymes (e.g., insulin, EPO, interferon, G-CSF and imiglucerase). Among monoclonal antibodies, the three most targeted products for biosimilars are rituximab, infliximab and adalimumab due to their high worldwide sales and approvals for multiple indications. Various key industry players in the generics market have started working on the manufacturing and clinical trials of MAbs. Bioexpress Therapeutic (Switzerland) has 16 biosimilar candidates of MAbs in the pipeline. Other major companies that have invested in the production of MAbs are Gene Techno Science (Japan), Celltrion (South Korea), Zydus Cadila (India), Biocon (India) and Samsung Biologics (South Korea). Across countries, China and India are considered attractive destinations for R&D outsourcing by foreign biosimilar manufacturing companies that are looking to reduce their growing R&D costs and increase the number of drug applications and approvals.

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<sup>21</sup> Lawrence, S (2016) Amgen partners with Daiichi on biosimilars after positive FDA panel. FierceBiotech, 14 July 2016, <http://www.fiercebiotech.com/biotech/amgen-partners-daiichi-biosimilars-after-positive-fda-panel>

<sup>22</sup> Calo-Fernandez, Bruno and Juan Leonardo Martinez-Hurtado (2012) Biosimilars: Company Strategies to Capture Value from the Biologics Market. *Pharmaceuticals* 2012, 5: 1393-1408; doi:10.3390/ph5121393

## Chapter Five

### Why Are Biologics and Biosimilars So Expensive?

UNLIKE in the case of SMDs where generic equivalents become available soon after the patents on these drugs expire (or in situations where the patent is not recognized in a particular territory), there is no effective competition in the market for biologics even in situations where the patents on the originator molecules have expired or are not granted. Contributing to this situation is what we described earlier – the complex structures of biologics and their dependence on relatively complex manufacturing processes involving living cells. This complexity introduces various barriers to competition in the market. Thus, in addition to intellectual property-related barriers (similar to what we see in the case of SMDs), early introduction of biosimilars also faces technological and regulatory barriers.

As a result, biologics are extremely expensive and consequently not easily accessible to patients, especially in low- and middle-income countries (LMICs). For example, one vial of adalimumab (for the originator product Humira from AbbVie) would cost about US\$1,000 – almost equivalent to the average annual wage in a low-income country. The high prices of biological drugs place a major burden on the public health budget of many LMICs which have introduced these drugs. For example, in 2015 biological drugs accounted for 35% of the pharmaceutical market in Colombia. Similarly in Brazil, while biological drugs account for 4% by volume of drugs distributed through its National Health System, they account for over half of the Ministry of Health's expenditure on medicines.<sup>23</sup>

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<sup>23</sup> Barry, F (2015) Filgrastim biosimilar is first Latin copy biologic, says Brazil. BioPharma Reporter, 24 November 2015, <http://www.biopharma-reporter.com/Markets-Regulations/Filgrastim-biosimilar-is-first-Latin-copy-biologic-says-Brazil>

The entry of biosimilars into the regulated markets of the EU and the US has also been very slow; biosimilars in 2014 accounted for less than 0.5% of the market for biological medicines.<sup>24</sup>

Even though biosimilar versions of many top-selling biological drugs are now being produced by non-originator companies, there are various factors that limit access to these. Current regulatory regimes require clinical trials to be done to establish that the biosimilar matches the potency, safety and efficacy of the originator. This requirement, together with the costly manufacturing processes, escalates the development costs for biosimilars. The estimated cost for development of a biosimilar is between US\$75-250 million, one order of magnitude higher than the cost for generics.<sup>25</sup>

Importantly, unlike in the case of the small molecule generic industry, many multinational pharmaceutical companies are entering the area of bio-generic manufacture. The latter have a stake in keeping the prices of biosimilars comparatively high, hence repeated industry-led assertions that biosimilar introduction will lead to only a modest drop of 10-50% in prices.<sup>26</sup> While different estimates exist regarding the cost of developing a biosimilar, the US Federal Trade Commission estimates the cost to be in the range of US\$100-200 million and development takes between 8-10 years (in contrast to 2-3 years for small molecule generics). The high investment and risk involved, it is said, would depress costs by only 10-35% compared with the cost of the originator biologic.<sup>27</sup> These assertions are however belied by other evidence – for example, the version of adalimumab produced by India's Zydus Cadila (Exemptia) led to an 80%

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<sup>24</sup> Dorey, Emma (2014) How the biologics landscape is evolving. *The Pharmaceutical Journal*, 17 November 2014

<sup>25</sup> Calo-Fernandez, Bruno and Juan Leonardo Martinez-Hurtado (2012) Biosimilars: Company Strategies to Capture Value from the Biologics Market. *Pharmaceuticals* 2012, 5: 1393-1408; doi:10.3390/ph5121393

<sup>26</sup> Mulcahy, AW, Z Predmore and S Matke (nd) The Cost Savings Potential of Biosimilar Drugs in the United States. Rand Corporation, [https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND\\_PE127.pdf](https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf)

<sup>27</sup> Dorey, Emma (2014) How the biologics landscape is evolving. *The Pharmaceutical Journal*, 17 November 2014

price reduction.<sup>28</sup> In Europe price drops in the range of 45-70% are already being seen in segments where there is competition from biosimilars.

Some analysts now say that the cost of developing a biosimilar is nearer US\$60 million. Of this, it is projected that US\$7-15 million is the typical cost of analyzing the originator molecule over a period of four years. Steinar Madsen of the Norwegian Medicines Agency posits that the cost of manufacture of a biologic is less than 10% of the market cost of the drug. It is also being projected that regulatory regimes will, in the near future, largely forgo the need to conduct expensive Phase III trials before biosimilars are approved, thus drastically cutting the cost of development of biosimilars.<sup>29</sup>

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<sup>28</sup> Press Trust of India (2014) Zydus Cadila launches biosimilar of AbbVie's Humira in India. *Economic Times*, 9 December 2014, [http://articles.economictimes.indiatimes.com/2014-12-09/news/56879703\\_1\\_rheumatoid-arthritis-first-biosimilar-humira](http://articles.economictimes.indiatimes.com/2014-12-09/news/56879703_1_rheumatoid-arthritis-first-biosimilar-humira)

<sup>29</sup> Stanton, Dan (2015) Number of biosimilar developers growing as costs plummet, say CPhI experts. 21 October 2015, <http://www.biopharma-reporter.com>

## Chapter Six

### **Biosimilars vs Generics of SMDs: Different Treatment by Regulators**

EXPERIENCE with SMDs tells us that the introduction of generic drugs (that is, copies of originator SMDs manufactured by non-originator companies) produces competition in the market, depresses prices and enhances access. A classic example is that of HIV medicines, the prices of which saw a 97.5% drop in the early 2000s after the introduction of generics by Indian companies. This has not happened in the case of biological drugs. As we discussed earlier, the complex high molecular weight and three-dimensional structures of biological drugs, their heterogeneity and dependence on production in living cells make it difficult to make exact copies.

Conventional generics are considered to be therapeutically equivalent to a reference once pharmaceutical equivalence (i.e., identical active substances) and bioequivalence (i.e., comparable pharmacokinetics) have been established. Generally, stringent clinical efficacy and safety studies are not required. In contrast, as we discuss later, in the case of biosimilars clinical trials to confirm safety and efficacy are demanded by regulatory bodies before they are provided with marketing approval. It is argued that the effects of a biological drug depend on its structural stability, and factors causing physical and chemical instability alter the three-dimensional structure and folding pattern of proteins, which may lead to changes in their immunogenic properties<sup>30</sup> – thus adding a new layer of complexity in testing for safety.

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<sup>30</sup> Undela, Krishna (2011) Biogenerics or Biosimilars: An overview of the current situation in India. *International Journal of Medical and Pharmaceutical Sciences* 1: 1-10, [https://www.researchgate.net/publication/236894615\\_Biogenerics\\_or\\_Biosimilar\\_s\\_An\\_overview\\_of\\_the\\_current\\_situation\\_in\\_India](https://www.researchgate.net/publication/236894615_Biogenerics_or_Biosimilar_s_An_overview_of_the_current_situation_in_India)

Here, it needs to be underlined that all medicinal products developed through biological processes do not pose the same level of complexity. In fact, 'similar' versions of biological drugs have been in the market for over five decades, for example in the case of penicillin, which is produced through fermentation technology. Likewise, vaccine manufacture is now undertaken by a number of companies other than the originator company. More recently, there have been several versions of human insulin available in the market. The discussions below on the challenges to biosimilar manufacture pertain to more recent biological drugs that use recombinant technology, and especially to monoclonal antibodies. These challenges are particularly relevant as the recent biologics of therapeutic importance fall in this category.

## Chapter Seven

### Technological Barriers to Manufacture of Biosimilars

A BIOSIMILAR has been defined as a biological medicine that has been proven, through a regulatory process, to have a high similarity to a reference biological medicine (also referred to as the originator or original biological medicine). A biosimilar's primary amino acid sequence matches that of the reference biological medicine with only minor differences in clinically inactive components. Biosimilars are approved by regulatory authorities to meet standards for similarity in quality, efficacy and safety to the reference biological medicine.<sup>31</sup>

The manufacturing of biologics using recombinant technology requires several stages of cell culture and purification, processes which are confidential to the company developing the product. As it is not possible for companies producing biosimilars to directly access this know-how, their manufacturing process will differ from that of the originator, and the structural variability of the product may be more pronounced. For example, different cell lines could alter the three-dimensional structure of the final product. These alterations can, theoretically, lead to adverse consequences for patient health, such as undesired immunogenic responses.<sup>32</sup>

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<sup>31</sup> International Union of Pure and Applied Chemistry (1997) *Compendium of Chemical Terminology*, 2nd edition. Cambridge Healthcare Institute

<sup>32</sup> Calo-Fernandez, Bruno and Juan Leonardo Martinez-Hurtado (2012) Biosimilars: Company Strategies to Capture Value from the Biologics Market. *Pharmaceuticals* 2012, 5: 1393-1408; doi:10.3390/ph5121393

It must be kept in mind, however, that all biological products are inherently variable due to the fact that they are produced from living organisms. This variability exists (even when the originator company manufactures the drug) within batches, from batch to batch, and when production processes are improved or changed or differ between manufacturers. Thus, what is rarely acknowledged is that different batches of biologics from innovator companies (branded biologics) also differ slightly.<sup>33</sup>

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<sup>33</sup> Welch, Anna Rose (2016) The Norwegian Biosimilar Phenomenon: From Biosimilar to 'Biogeneric'. *Biosimilar Development*, 26 July 2016, <http://www.biosimilardevelopment.com/doc/the-norwegian-biosimilar-phenomenon-from-biosimilar-to-biogeneric-0001>

## Chapter Eight

# Barriers Related to Intellectual Property Rights and Data Exclusivity

BIOLOGICAL drugs are protected by patents (on both product and process), trade secrets and data exclusivity. Unlike in the case of SMDs, process patents can act as a major barrier to the introduction of biosimilars. Due to the large-molecule nature of biologic products, product patent protection is often narrower than that for small molecule drugs. The significant molecular size of biologic products makes it easier to ‘invent around’ an existing patent, thus narrowing the extent of coverage by a product patent.<sup>34</sup> Thus, process patents are proportionally more important.

Patents constitute the first-level barrier to the entry of biosimilars. Much of the recent interest in biosimilar development is being driven by the fact that several top-selling biologics have recently lost patent exclusivity or are poised to lose it soon. The combined value in 2015 of eight top-selling biologics losing exclusivity protection from patents or other measures between 2015 and 2020 in France, Germany, Italy, Spain and the UK, as well as the US, was €42.3 billion.<sup>35</sup> This includes one of the world’s biggest-selling drugs of all time, AbbVie’s Humira (adalimumab), which had sales of €10.8 billion in five EU countries and the US, and which loses exclusivity in the EU in 2018 and in the US in 2016. Similarly, Amgen and Pfizer’s Enbrel (etanercept), which is used in the treatment of a number of chronic inflammatory conditions and which earned €6.9 billion in

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<sup>34</sup> Gliberman, Steven (ed) (2016) *Intellectual Property Rights and the Promotion of Biologics, Medical Devices, and Trade in Pharmaceuticals*. Fraser Institute, <http://www.fraserinstitute.org>

<sup>35</sup> Brennan, Zachary (2016) IMS: Biosimilars Could Save Up to \$110B in EU, US Through 2020. 29 March 2016, <http://www.raps.org/Regulatory-Focus/News/2016/03/29/24671/IMS-Biosimilars-Could-Save-Up-to-110B-in-EU-US-Through-2020/>

the EU and the US, has lost exclusivity in the EU. Sanofi-Aventis' diabetes drug Lantus (insulin glargine), which had sales of €8.7 billion in the EU and the US last year, lost exclusivity in the EU in 2014 and in the US in 2015.<sup>36</sup>

<b>Drug</b>	<b>Ingredient</b>	<b>Company</b>	<b>Indication</b>	<b>EU patent expiry</b>	<b>US patent expiry</b>
Humira	Adalimumab	AbbVie	Autoimmune disorders	2018	2016
Lantus	Insulin glargine	Sanofi	Diabetes	2014	2015
Enbrel	Etanercept	Amgen	Autoimmune disorders	2015	2028
Remicade	Infliximab	Johnson & Johnson	Autoimmune disorders	2015	2018
MabThera	Rituximab	Roche	Cancers; autoimmune disorders	Expired	2018
Avastin	Bevacizumab	Roche	Cancers	2019	2019
Herceptin	Trastuzumab	Roche	Breast cancer	2014	2019
Avonex/ Rebif	Interferon Beta -1A	Biogen/ Pfizer	Multiple sclerosis	2015	2016
Copaxone	Glatirameracetate	Teva	Multiple sclerosis	2017	2014
Neulasta	Pegfilgastrim	Amgen	Adjunct to cancer chemotherapy	2015	2015
Lucentis	Ranibizumab	Genentech	Macular degeneration	2016	2016

Concurrently, an estimated 30 companies are actively developing biosimilars, particularly for infliximab, etanercept, rituximab and adalimumab.<sup>38</sup>

However, even after originator biologics lose patent exclusivity, trade secrets can continue to create barriers to the entry of biosimilars. Most

<sup>36</sup> Ibid.

<sup>37</sup> See: [http://whocc.goeg.at/Downloads/Conference2015/Presentations/DI/1030\\_strandI\\_Vulto.pdf](http://whocc.goeg.at/Downloads/Conference2015/Presentations/DI/1030_strandI_Vulto.pdf)

<sup>38</sup> Ibid.

small molecule drugs can be easily manufactured once their chemical structure is known. However, because of the complexity of producing biologics, companies guard the specifics of their manufacturing and scale-up methods as trade secrets. This forces biosimilar manufacturers to develop their own methods of manufacture and subsequent validation (to show similarity with the originator when applying for marketing approval), often at great expense.<sup>39</sup>

Industry sources also assert that product and process patents are inadequate (or less effective as compared with the case of SMDs) in protecting the intellectual property of the innovator firm's safety and efficacy data. Thus data exclusivity provisions are demanded to enhance protection for innovator drugs.<sup>40</sup> Such provisions are 'TRIPS-plus', i.e., not required by the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). The importance assigned to data exclusivity provisions by innovator biotech companies was evident in the protracted negotiations on the issue during the discussions on the Trans-Pacific Partnership (TPP) free trade agreement. The United States (among others) bargained very hard for the introduction of a special protection period of 12 years' exclusivity for biologics,<sup>41</sup> which was opposed by Australia and New Zealand. The final agreement requires countries to implement one of two options: (1) give eight years of market exclusivity from the date the biologic is approved in the country concerned; or (2) give five years of market exclusivity from the date the

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<sup>39</sup> Sherkow, Jacob S (2016) Protecting products versus platforms. <http://www.nature.com/bioent/2016/160401/full/bioe.2016.4.html>

<sup>40</sup> Lybecker, KM (2016) The Biologics Revolution in the production of drugs. Fraser Institute, July 2016, <https://www.fraserinstitute.org/sites/default/files/biologics-revolution-in-the-production-of-drugs.pdf>

<sup>41</sup> Jackson, T and D Koedyk (2015) Piggy-backing to market? TPP negotiations bring data exclusivity periods of biologics into public spotlight. *Baldwins*, 7 September 2015, <https://www.baldwins.com/news/piggy-backing-to-market-tpp-negotiations-bring-data-exclusivity-periods-of>

biologic is approved in the country concerned and other measures to deliver a comparable market outcome. It is argued by a number of TPP governments, such as Australia, New Zealand, Chile and Singapore, that the provision does not require countries to grant more than five years of biologic exclusivity.<sup>42</sup>

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<sup>42</sup> E.g., Australia: <http://dfat.gov.au/trade/agreements/tpp/outcomes-documents/Pages/outcomes-biologics.aspx>; New Zealand: [http://tpp.mfat.govt.nz/assets/docs/TPP\\_factsheet\\_Intellectual-Property.PDF](http://tpp.mfat.govt.nz/assets/docs/TPP_factsheet_Intellectual-Property.PDF); Chile: <https://ustr.gov/about-us/policy-offices/press-office/speechestranscripts/2015/october/transcript-trans-pacific>; Singapore: <https://www.politicopro.com/trade/story/2015/10/pro-trade-tppbiologics-behsudi-059493>.

## Chapter Nine

# The Evolving Regulatory Landscape for Approval of Biosimilars

WHILE the early introduction of cheaper biosimilars faces intellectual property and technological hurdles, the regulatory barriers imposed by regulatory agencies in different countries are currently the most significant. WHO's role in this has been less than facilitative and its conservative approach has had a chilling effect on the early introduction of biosimilars.

Since the late 1990s, non-originator biological products have been known by different names, viz., follow-on biologics, bio-generics, biosimilars, etc. Generally speaking, these nomenclatures are closely linked to the regulatory pathways followed for the approval of these products. Interestingly, regulatory pathways for non-originator biological products were recognized in many Asian countries (India, South Korea, etc.) as early as the 1990s, that is, much before regulatory pathways existed in the EU and the US. Thus non-originator biological products were available in countries such as India a decade or more before their entry into the European market.

The regulatory pathway followed initially in Asian countries was different from the biosimilar regulatory pathway broadly advocated by the International Conference on Harmonization (ICH), a closed regulatory standard-setting body founded by drug regulatory authorities of the EU (European Medicines Agency – EMA), Japan (Ministry of Health, Labour and Welfare – JMHLW) and the US (Food and Drug Administration – US FDA) and the originator pharmaceutical industry associations of those countries (the European Federation of Pharmaceutical Industries' Associations – EFPIA; the Japan Pharmaceutical Manufacturers Association –

JPMA; and the Pharmaceutical Research and Manufacturers of America – PhRMA). Positions that the ICH promotes are reflective of the interests of originator companies.<sup>43</sup>

Biosimilars, including monoclonal antibodies, received regulatory approval in India and South Korea much before the developed-country markets. To date, India has approved more than 50 ‘similar biologic’ products for its market. By contrast, the more stringent requirements of ICH-aligned countries (mainly developed countries) have limited approvals so far. Till 2015 Australia had approved eight, Japan had approved seven and Canada three.<sup>44</sup> The EU had approved about 24, while the US approved its first biosimilar for filgrastim in 2015. In June 2013, the first approval for a biosimilar monoclonal antibody was granted in the EU for infliximab.<sup>45</sup>

The Indian guidelines for introduction of biosimilars were modified in 2012. Prior to 2012 the guidelines were less onerous on biosimilar manufacturers. See Table 5 for important divergences between the pre-2012 regulations in India and the WHO guidelines (see below). The 2012 guidelines in India were modelled on the then existing EMA guidelines and the WHO guidelines,<sup>46</sup> thus drastically reducing the divergences. The guidelines were further modified in 2016.<sup>47</sup>

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<sup>43</sup> Third World Network (2014) WHO: Alliance with industry raises concerns over medicine regulation. TWN Info Service on Health Issues, 20 May 2014, <http://www.twn.my/title2/health.info/2014/hi140502.htm>

<sup>44</sup> Scott, Cheryl and S Anne Montgomery (2015) Biosimilars and Biobetters Offer Unique Benefits – and Risks. 16 June 2015, <http://www.bioprocessintl.com>

<sup>45</sup> Generics and Biosimilars Initiative (2018) Biosimilars approved in Europe. 2 February 2018, <http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe>

<sup>46</sup> Ohly, C (2012) The New India Guidelines on Similar Biologics: Regulatory and Market Authorization Requirements. Spicy IP, <https://spicyip.com/2012/10/guest-post-new-india-guidelines-on.html>

<sup>47</sup> Generics and Biosimilars Initiative (2017) India updates its similar biologics guidelines. <http://www.gabionline.net/Guidelines/India-updates-its-similar-biologics-guidelines>

<b>Table 5: Important divergences between pre-2012 Indian guidelines and WHO guidelines<sup>48</sup></b>	
<b>Pre-2012 Indian guidelines</b>	<b>WHO guidelines</b>
Comparative PK/PD is not mandatory	Comparative PK/PD is required
Comparative CT is not mandatory	Comparative CT is required
Extrapolation to other indication can be obtained	Extrapolation to other indication can be approved only if the mode of action is similar
Immunogenicity is not mandatory, but expected	Immunogenicity is mandatory

Notes: PK: pharmacokinetic; PD: pharmacodynamic; CT: clinical trials

### ***WHO's guidelines and resolution at the WHA***

In 2009 the WHO Expert Committee on Biological Standardization adopted Guidelines on Evaluation of Similar Biotherapeutic Products. These guidelines drew heavily from the broad positions advocated by the ICH and since then there has been a major push for the adoption in other countries of biosimilar guidelines modelled on the ICH's positions and EU guidelines. (The EU guidelines have since been modified and are now much less onerous (see below).) The 2009 WHO guidelines require 'head to head' comparability of the non-originator product with the originator product.

The principles underlying the approach to biosimilars included in the WHO guidelines are:<sup>49</sup>

- Full quality dossier, including comparisons with original
- Limited preclinical dossier including pharmacokinetics comparison with original
- Clinical similarity where hard clinical endpoint is not needed
- Extrapolation possible
- Post-marketing safety studies including immunogenicity.

<sup>48</sup> Malhotra, H (2011) Biosimilars and non-innovator biotherapeutics in India: An overview of the current situation. *Biologicals* 39 (2011): 321-324, <https://www.ncbi.nlm.nih.gov/pubmed/21784652>

<sup>49</sup> See: [http://bcn2012.europeanbioanalysisforum.eu/slides/day%202/ii%20biosimilars/1\\_schellekens.pdf](http://bcn2012.europeanbioanalysisforum.eu/slides/day%202/ii%20biosimilars/1_schellekens.pdf)

Demonstration of similarity with the originator requires comparative clinical trials with the originator. According to industry sources, a major proportion of the biosimilar development cost arises as a result of the need to purchase the originator product. Further, the burden of proof on similarity also increases the duration of biosimilar development. These onerous regulatory requirements delay introduction of biosimilars and prevent a significant drop in prices when biosimilars are introduced. Thus regulatory requirements represent one of the most significant barriers to affordable access to biological products. Also, even with the smaller clinical trials that are demanded by current regulations, biosimilar sponsors face challenges in identifying clinical sites and investigators that understand their unique development issues and can attract a sufficient number of participants.<sup>50</sup>

The WHO guidelines have been criticized by analysts for their ‘similarity proof requirement’: ‘Biosimilars regulatory guidance should be reviewed in light not only of the scientific and regulatory experience gained over time, but also of the needs and interests of national health systems and pharmaceutical markets in low-resource countries. Stringent regulatory authorities such as EMA have already begun to waive requirements for comparability exercise at clinical level under appropriate circumstances. This approach is supported by academic experts who claim that non-comparative clinical trials are sufficient for regulatory purposes, and who call for pragmatic approaches focused primarily on the patients clinical outcomes and on scientific principles, using the state-of-the-art tools.’<sup>51</sup>

Reflecting the concerns on non-availability of biological products at affordable prices, WHO’s governing World Health Assembly (WHA) in 2014 adopted a resolution that urged member states ‘to work to ensure that the introduction of new national regulations, where appropriate, does

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<sup>50</sup> Wechsler, J (2016) Biosimilar trials differ notably from innovator studies. <http://www.appliedclinicaltrials.com/biosimilar-trials-differ-notably-innovator-studies>

<sup>51</sup> Milani, B and S Gaspani (2013) Pathway to affordable, quality based sources of pegylated interferon alpha for treating Hepatitis C. *Generics and Biosimilars Initiative Journal*, Volume 2, 2013, Issue 4, p. 194, <http://apps.who.int/medicinedocs/documents/s21311en/s21311en.pdf>

not constitute a barrier to access to quality, safe, efficacious and affordable biotherapeutic products, including similar biotherapeutic products'.<sup>52</sup> The resolution further requested the WHO Director-General 'to convene WHO's Expert Committee on Biological Standardization to update the 2009 guidelines, taking into account the technological advances for the characterization of biotherapeutic products and considering national regulatory needs and capacities and to report on the update to the [WHO] Executive Board'.

However, WHO does not seem to have followed the spirit of the WHA resolution. Instead, it has, on its website, issued certain 'clarifications' in the form of Q&As.<sup>53</sup> Thus WHO has not actually updated its 2009 guidelines. It has issued several reports by its Expert Committee on Biological Standardization which continue to strengthen the obligations of biosimilar manufacturers laid out in the 2009 guidelines. A report by the expert committee issued in 2016 recommends reappraisal or re-registration of products introduced in situations where the WHO guidelines were not followed.<sup>54</sup> The 2016 report recommends, inter alia, that: 'Attention should be paid to any key differences between national requirements and the WHO Guidelines – such as the lack of a head-to-head comparability exercise for an SBP [similar biotherapeutic product]. The NRA [national regulatory authority] should provide manufacturers with a critical dataset for the re-registration of such products. Changes in regulatory requirements may be needed, as well as amendments to the legal framework of the country concerned, to enable such new requirements to be implemented.'

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<sup>52</sup> World Health Organization (2014) Sixty Seventh World Health Assembly, Resolutions and Decisions Annexes, p. 68, [http://apps.who.int/gb/ebwha/pdf\\_files/WHA67-REC1/A67\\_2014\\_REC1-en.pdf#page=25](http://apps.who.int/gb/ebwha/pdf_files/WHA67-REC1/A67_2014_REC1-en.pdf#page=25)

<sup>53</sup> See: [http://www.who.int/biologicals/QA\\_for\\_SBPs\\_HK\\_12\\_Dec\\_2017\\_\(2\).pdf?ua=1](http://www.who.int/biologicals/QA_for_SBPs_HK_12_Dec_2017_(2).pdf?ua=1)

<sup>54</sup> World Health Organization (2016) WHO Expert Committee on Biological Standardization, sixty-sixth report. WHO technical report series No. 999, [http://www.who.int/biologicals/expert\\_committee/WHO\\_TRS\\_999\\_corrigena\\_web.pdf](http://www.who.int/biologicals/expert_committee/WHO_TRS_999_corrigena_web.pdf)

## *European guidelines*

In October 2014 the EMA finalized new regulatory guidelines on biosimilars in the EU.<sup>55</sup> The guidelines update its October 2005 guidelines on biosimilarity (developed based on ICH standards), which officials said had become outdated. The new guidelines, it is claimed, would clarify how companies can establish biosimilarity between their follow-on biologic and the original biologic product approved by the EMA. The guidelines also include a discussion regarding the ‘principles of establishing biosimilarity’. The EMA recommends a ‘stepwise approach’ meant to build upon rigorous data at every stage of the evaluation process. The EMA explains: ‘If the biosimilar comparability exercise indicates that there are relevant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development to support a full Marketing Authorisation Application (MAA) should be considered instead ... Clinical data cannot be used to justify substantial differences in quality attributes.’<sup>56</sup> Essentially what this stepwise approach involves is an assessment of similarity at every step. If, at any step, the divergence in similarity is seen to be too large, the similar molecule will be treated as a new molecule requiring submission of a full dossier.

## *US guidelines*

At the end of March 2010 the United States enacted the Biologics Price Competition and Innovation Act (BPCI). The BPCI defines a biosimilar product as ‘(A) ... highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B) ... no clinically meaningful differences between the biological product and the ref-

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<sup>55</sup> The EMA guidelines can be accessed here: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000408.jsp&mid=WC0b01ac058002958c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c)

<sup>56</sup> See: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/10/WC500176768.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf)

erence product in terms of the safety, purity, and potency of the product'.<sup>57</sup> As regards interchangeability between originator products and biosimilars, the Act says that the interchangeable product must meet all the same requirements as a reference product and in addition have the same route of administration, dosage form and strength as the reference product.<sup>58</sup> In many states in the US, an interchangeable may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product, as this is governed by state pharmacy laws. The US FDA states in this respect: 'Once a biosimilar has been approved by FDA, patients and health care providers can be assured of the safety and effectiveness of the biosimilar, just as they would for the reference product.'<sup>59</sup>

There are no fundamental differences between the EU and US guidelines concerning the non-clinical and clinical testing strategies. However, extrapolating immunogenicity data from one indication to another is allowed in the US but not in the EU. The European Commission issued a directive in 2012 requiring biological products to be identified by brand name and not by INN. However, the US FDA is less precise in this context, saying only that the naming and labelling of the drug should facilitate decision making by the prescribing healthcare professional.<sup>60</sup>

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<sup>57</sup> Lemery, SJ, FJ Esteva and M Weise (2016) Biosimilars: Here and Now. *Am Soc Clin Oncol Educ Book* 2016; 35: e151-e157; doi: 10.14694/EDBK\_155954. <https://meetinglibrary.asco.org/record/50599/edbook#fulltext>

<sup>58</sup> See: <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM606115.pdf>

<sup>59</sup> See: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580430.htm#sub>

<sup>60</sup> Blank, Tobias (2013) Safety and toxicity of biosimilars – EU versus US regulation. *Generics and Biosimilars Initiative Journal* 2013; 2(3): 144-150; doi: 10.5639/gabij.2013.0203.039

## Chapter Ten

### How Necessary Are Present Requirements to Establish Similarity?

SEVERAL experts have argued that the merits and/or added value of the comparability exercise are questionable as the comparison of quality characteristics between the biosimilar and the reference product will always show differences. It is further argued that there are also many reasons to question the usefulness of comparative pharmacokinetic trials. ‘The assays to determine product levels are often too imprecise; the relation between pharmacokinetic parameters and clinical effect of biologics is unclear; the dose-response curve of therapeutic proteins is often bell-shaped (meaning that widely differing protein levels have the same clinical effect); and the acceptance range for pharmacokinetics parameters between biosimilar and reference product are difficult or impossible to predefine and justify ... Dropping the obligation to do the comparability exercise will make it easier to develop more complex biosimilars, such as monoclonal antibodies (mAbs) and vaccines.’<sup>61 62</sup>

Moreover, the value of comparative clinical trials for showing clinical equivalence of biosimilars that demonstrate a high degree of similarity in physical, chemical, structural and biological characteristics with the original product is increasingly being questioned, and advances in analytical methods that provide robust non-clinical data should reduce the need for extensive clinical comparison.<sup>63</sup>

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<sup>61</sup> Schellekens, H and E Moors (2010) Clinical comparability and European biosimilar regulations. *Nature Biotechnology* 28: 28-31

<sup>62</sup> Frapaise FX (2018) The End of Phase 3 Clinical Trials in Biosimilars Development?. *BioDrugs*, August 2018

<sup>63</sup> Schellekens, H et al. (2016) Safety and efficacy of biosimilars in oncology. *The Lancet*, [http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045\(16\)30374-6.pdf](http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(16)30374-6.pdf)

## Chapter Eleven

### **Uptake of Biosimilars in Clinical Practice: Interchangeability and INN**

THE role of regulatory agencies is also critical in the uptake of biosimilars in clinical practice. In the EU, different countries have differing approaches to the issue of interchangeability between biologics and biosimilars. Most EU member states do not explicitly authorize the substitution of biologicals from different manufacturers, and a number have gone as far as banning this practice.<sup>64</sup> However, Norway has emerged as a leader in the introduction of biosimilars in the EU, led by Dr. Steinar Madsen of the Norwegian Medicines Agency.

Europe saw the approval of Omnitrope, its first biosimilar, in 2006. Shortly thereafter came the rise of what Madsen referred to as the ‘biosimilar resistance’. EU countries encountered numerous claims that biosimilars were inferior products and, therefore, that ‘switching’ (that is, interchangeability between higher-cost biologics and lower-cost biosimilars) should not be permitted. However, Norway encouraged switching and the results were often dramatic. In Norway the biosimilar infliximab (Remsima) has a 92.9% market share (April 2016). Other Scandinavian countries have followed suit; in Denmark, the biosimilar of infliximab has 96% of the market, and in Finland 88%. In the absence of similar strategies in Sweden, biosimilars account for just 33.5% of the market.<sup>65</sup>

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<sup>64</sup> \_\_\_\_\_ (2015) Biosimilars and interchangeability. Generics and Biosimilars Initiative, 13 November 2015, <http://www.gabionline.net/Biosimilars/Research/Biosimilars-and-interchangeability>

<sup>65</sup> Welch, Anna Rose (2016) The Norwegian Biosimilar Phenomenon: From Biosimilar To ‘Biogeneric’. *Biosimilar Development*, 26 July 2016, <http://www.biosimilardevelopment.com/doc/the-norwegian-biosimilar-phenomenon-from-biosimilar-to-biogeneric-0001>

Likewise in the US, a number of states have passed legislation that requires a biosimilar to be deemed by the FDA to be interchangeable before a pharmacist can automatically substitute a biosimilar for a biologic. No interchangeable biosimilars have been approved in the US as yet.<sup>66</sup>

In 2015, the Australian regulatory authorities made the world's first recommendation to allow clinicians and pharmacists the option of substituting expensive biologic medicines at the chemist's if there is a cheaper replacement or biosimilar available that has been determined by experts to be a safe, equally effective treatment. The recommendation does not require that pharmacists notify physicians or patients of a substitution, nor does it specify that pharmacists must keep a log of the substitution.<sup>67</sup>

How biosimilars are named also has an impact on the willingness of physicians to switch between branded biologics and biosimilars. While in the case of small molecule drugs generic equivalents are given the same INN as the innovator drugs, there is no uniformity regarding this across various regulatory regimes for biological products.

WHO's INN Expert Group has proposed the use of a Biological Qualifier (BQ), separate from the INN scheme, to identify the source of a biological substance to 'enable substances to be traced in different licensing systems, whether classified as "similar biological substances" or not'.<sup>68</sup> Consisting of four random consonants and an optional two-digit checksum, the BQ is proposed as an identifier that follows the non-proprietary name of each biologic and biosimilar product. This recommendation is in fact

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<sup>66</sup> Brennan, Zachary (2016) IMS: Biosimilars Could Save Up to \$110B in EU, US Through 2020. 29 March 2016, <http://www.raps.org/Regulatory-Focus/News/2016/03/29/24671/IMS-Biosimilars-Could-Save-Up-to-110B-in-EU-US-Through-2020/>

<sup>67</sup> Hernandez, R (2015) Australia Allows Pharmacy-Level Substitution of Biologics. <http://www.biopharminternational.com/australia-allows-pharmacy-level-substitution-biologics>

<sup>68</sup> World Health Organization (2016) International Nonproprietary Names (INN) for biological and biotechnological substances (a review). <http://www.who.int/medicines/services/inn/BioReview2016.pdf?ua=1>

contrary to the recommendation of an informal consultation in 2006 convened by WHO. This consultation recommended: ‘INN should be based, as now, on considerations of molecular characteristics and pharmacological class. No specific process should be introduced for naming biosimilars.’<sup>69</sup>

Biosimilar manufacturers argue that distinct names will impede the adoption of biosimilars.<sup>70</sup> Currently WHO has shelved the proposal on BQs, but it could be resurrected at a later date at the behest of some WHO member states which choose to side with industry.

The resistance towards substitution of innovator biologics with biosimilars, including in the medical profession, stems from the notion that, given the unique characteristics of biological drugs, copies in the form of biosimilars simply will not be able to match the originator. However, some recent research seems to suggest that biosimilars appear to be as good as the originator biologics. A recent study reviewed data from 19 studies conducted through April 2016, which compared biologic and biosimilar versions of tumour necrosis factor-alpha (TNF- $\alpha$ ) inhibitors. These treatments suppress the over-activity of the immune system in rheumatoid arthritis, inflammatory bowel disease (such as Crohn’s disease) and psoriasis. They include well-known biologics – Amgen’s Enbrel, AbbVie’s Humira, and Johnson & Johnson’s Remicade. The findings, published in the *Annals of Internal Medicine*, suggest that the biosimilar forms of TNF- $\alpha$  inhibitors are just as safe and effective as their biologic counterparts.<sup>71</sup>

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<sup>69</sup> See: [http://www.who.int/medicines/services/inn/BiosimilarsINN\\_Report.pdf](http://www.who.int/medicines/services/inn/BiosimilarsINN_Report.pdf)

<sup>70</sup> Li, S and I Royzman (2016) Final WHO Biosimilar Naming Proposal Resembles FDA Approach. *Biologics Blog*, 3 February 2016, <https://www.biologicsblog.com/final-who-biosimilars-naming-proposal-resembles-fda-approach>

<sup>71</sup> Guzowski, S (2016) How do biosimilars compare with brand-name biologics? <http://www.ddmag.com/article/2016/08/how-do-biosimilars-compare-brand-name-biologics>

## Chapter Twelve

### Conclusions

THIS paper has discussed the ecosystem that informs access to biological drugs, including biosimilars. The analysis carried out in the paper leads us to the following conclusions and recommendations:

- The potential role of biological drugs in promoting real therapeutic advances needs a deeper analysis. However, current evidence suggests that they will play an increasingly major role in the future in advancing therapeutic outcomes for several autoimmune and degenerative diseases and in cancer treatment.
- Biological drugs are extremely expensive. Their high prices are a reflection of protected monopolies in the biotech sector. Further, unlike in the case of SMDs, the anticipated drop in prices after introduction of biosimilars is conventionally pegged at only around 30%. There are no clear technical reasons why price drops cannot be much sharper.
- Regulatory barriers (i.e., onerous requirements for regulatory approval) are key factors preventing introduction of cheaper follow-on products of equivalent safety and efficacy. The current regulatory regimes and the underlying WHO guidelines are not in sync with advances in the science of biological products. Insistence, by regulatory agencies and in the WHO guidelines, on head-to-head comparisons, including comparative pharmacokinetic studies, between innovator products and follow-ons is no longer justifiable. Moreover, it is possible to obviate the need for expensive and difficult-to-design clinical trials given better techniques for characterization of follow-ons, which could be combined with animal stud-

- ies. Regulatory regimes and guidelines, including the WHO guidelines, need to be revised taking the above into account.
- Given monopolies enjoyed by innovator biologics and their very high market prices, there appears to be little incentive available to reduce the cost of manufacture of biological products through introduction of more efficient technologies. On the other hand, the manufacturers of follow-on products appear better placed to introduce more efficient and cheaper technologies.
  - Intellectual property protection, just as in the case of SMDs, promotes monopolies and prevents the early introduction of follow-on biologics. Process patents and trade secrets are major barriers to the introduction of biosimilars. In addition, the biotech industry is more aggressive in demanding data exclusivity rules. All these act as layers of barriers to the early introduction of cheaper biosimilars.
  - The proposed introduction of ‘Biological Qualifiers’ to be tagged on to INNs for biosimilars is unjustified and WHO should not pursue this proposal.
  - It is necessary to harmonize rules and allow for interchangeability between innovator products and biosimilars which have received regulatory approval. This would make uptake of biosimilars in clinical practice easier.



**THIS PAPER** examines the landscape of biological medicines and locates this analysis in the characteristics of biological drugs which set them apart from small molecule drugs. These characteristics impact on the way biological drugs are manufactured; on the development of follow-on versions of innovator biological drugs; on the way biological drugs – both innovators and follow-ons – are regulated; on the way these drugs are protected by different kinds of intellectual property rights and data protection mechanisms; and on the opportunities and challenges in the introduction of biological drugs, including biosimilars, in a range of countries.

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