

DIFFERENCES IN BIOSIMILARS APPROVAL BETWEEN THE USA AND EUROPEAN UNION

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Abstract

Biosimilar reviews and approvals have significant structural differences that contrast Europe and the United States. Regulatory processes and market subtleties create a divergence of the markets. This paper will review market differences between Europe and the USA and evaluate strengths and weaknesses between the two systems. The study explores the differences in terms of the approval times for the biosimilars, the differences in intellectual property rights, the effects that expiring and extended biologic patents have on the entry of biosimilars, and the effects that lawsuits have on the approval process. There are various examples from Europe that the USA could consider embracing that would lead to lower biosimilar and biologics pricing. Particularly, policy changes aimed to encourage the healthcare industry to help educate the public to address false notions of biosimilar's effectiveness and safety as well as increasing incentives for prescriptions to include biosimilars in lieu of biologics to aid in equalizing market pricing.

Keywords: biologics; biosimilars; intellectual property; market pricing.

1. INTRODUCTION

The regulatory framework for biosimilars in Europe is European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP), which was established in the year 2005. CHMP initially assesses new medicines for approval in the market before the central approval is carried out by EMA. It is, therefore, the body charged with authorizing new medicine or drug applications before their approval, even though some authorizations become withdrawn after the EMA approves them (Figg et al., 2019). In the USA, the regulatory framework is established by the Biologics Price Competition and Innovation Act (BPCIA) of 2009, which shows why the country has trailed its European counterparts in approving biosimilars and biologics. The USA Food and Drug Administration (FDA) performs the assessments, authorization, and approval of the new drugs for entry into the market. There are marked differences between the approval processes in the USA and Europe through the policies and procedures that the EMA and the BPCIA specify. This paper explores the differences in terms of the approval times for the biosimilars, the differences in intellectual property rights, the effects that expiring and extended biologic patents have on the entry of biosimilars, and the effects that lawsuits have on the approval process.

2. APPROVAL TIMES FOR BIOSIMILARS

The differences between the USA and European regulatory frameworks and processes for biosimilars introduce variations in the duration it requires for the agencies to approve the biosimilars. A GaBI Journal (2020) special report highlighted the differences between the USA and European Union (EU) biosimilars markets in terms of the time taken to authorize or recommend the approval of biosimilars through the study of nine specific

products. It is worth noting that the first biosimilar was approved in the EU in the year 2006, while the first approval of a biosimilar in the USA occurred in 2015 (Figg et al., 2019). Consequently, the approval of biosimilars in the USA lagged the European approvals for a long time. For instance, the EMA approved Filgrastim on September 15, 2008, for low neutrophil count indicators, a biosimilar that the FDA approved six and a half years later in March 2015 (GaBI Journal Editor, 2020). Similarly, the FDA only came to approve Epoetin alfa, a biosimilar for treating anemia, 10.7 years after the EMA had first approved it in August 2007. However, the USA has made attempts to catch up with the EU in terms of the approval of biosimilars, but FDA still lags its European counterpart in the process. For instance, the EMA approved the first biosimilar for Infliximab, used for autoimmune diseases, in September 2013, 2.6 years before the FDA approved it in April 2016 (GaBI Journal Editor, 2020). The first biosimilar for Rituximab, used for autoimmune disease and cancer, got its approval in Europe in February 2017 but was only approved in November 2018 – 1.8 years later – in the USA. The time taken for approval has decreased further for some specific biosimilars. For instance, the EMA approved the biosimilar for Etanercept, used for autoimmune diseases such as arthritis, in January 2016, while the FDA approved it 7.2 months later in August 2016 (GaBI Journal Editor, 2020). The FDA similarly approved biosimilars for Adalimumab (for treating autoimmune disease) and Pegfilgrastim (for managing low neutrophil count) six months after the EMA had first approved them. The case of Trastuzumab – used in treating breast cancer – shows that the FDA is catching up with the EMA in terms of the time taken before approval. The EMA approved the biosimilar in Europe on November 25, 2017, only five days before the FDA approved it in the USA on December 1, 2017.

The history of these biosimilars shows the disparities in the approval times between the regulatory frameworks in the USA and EU. From a review of 16 biosimilars and their regulatory approval and submitted clinical trials, Jung et al. (2020) noted that 10 of the biosimilars were approved first by EMA in the EU at a median duration of 18 months before FDA made similar approvals in the USA. The authors note that in five cases, the same clinical trials were submitted to the FDA and the EMA, yet the latter approved four of them first before the FDA had approved its first (Jung et al., 2020). The differences in time could be explained by the differences in the rigors that the agencies adopt in the assessment and approval processes, with the FDA seemingly more rigorous in the considerations that it makes before approving biosimilars. Jung et al. (2020) report that the applicants for 10 biosimilars submitted 36 clinical trials along with their applications to EMA before they could obtain approval. For the same applications, the number of trials submitted to the FDA was 44, implying that the agency required more demonstrations of the efficacy of the new products before they could approve them. Furthermore, the median number of participants involved in the clinical trials to the EMA was 153 as compared to the 352 in the trials submitted to the FDA.

There are cases, however, where the FDA approves biosimilars faster than the EMA. The USA outperformed the EU in the year 2019 after making 10 approvals (Harston, 2021). From Jung et al.'s (2020) study, six of the 16 biosimilars received FDA approvals at a median time of six months before the EMA followed up with approval. In five of the cases, the applicants submitted the same clinical trials to the agencies, with the FDA

receiving 20 clinical trials as compared to the EMA's 22 clinical trials (Jung et al., 2020). The number of participants in the submitted trials was also higher for EMA as compared to the FDA. The trend shows that the disparity in the approval times is associated with the requirements that the agencies need the applicants to meet before making their approvals. The FDA has, however, historically demanded more intensive testing of the product before it can be approved. It is worth noting that five biosimilars were second-to-market products, with first biosimilars for the same biologic had either FDA or EMA approval (Jung et al., 2020).

The implication is that the duration of approval is faster if there is prior approval for an originator biologic. Recent trends show that the FDA has streamlined its approval process for biosimilars and is recently approving the drugs faster than the EMA does. Jung et al. (2020) note that the FDA approves biosimilars several months before the EMA, and even grants approvals for certain second-to-market biosimilar products backed by only phase I trials – without the need for phase II or III trials. The process of approvals for biosimilars in the EMA still follows the same principle – demonstration of its similarity to an originator biologic, with evidence provided for the safety, quality, and efficacy of the new product (Schiestl et al., 2017). The process does not require a clinical research program that is as thorough and detailed as that which is required for an originator biologic. The EMA has guidance that allows manufacturers to conduct clinical trials for new biosimilars using reference medicines that are authorized outside the European Economic Area (EEA) during the filing for EU approvals (Schiestl et al., 2017). These requirements provide some backing for the relatively fast turnaround of the EMA approval process.

Despite the recent advances that the FDA has made with the approval speed, the number of biosimilars approved in the EU within a year is still significantly higher than that of those approved in the USA. For instance, while highlighting the differences, the GaBI Journal (2020) reported that at the end of 2019, the total number of approved biosimilars was 26 in the USA as compared to the 58 total number of biosimilars in the EU. The disparity could be explained by the fact that the EU started biosimilar approvals considerably long before the USA followed suit. The trend could also be explained by the fact that FDA only approved three biosimilars in 2020 and have made no approvals in 2021 (Harston, 2021). During the same period, the EMA has made four approvals and withdrawn approvals for two other biosimilars.

3. INTELLECTUAL PROPERTY RIGHTS FOR BIOSIMILARS

The intellectual property rights of the developers of the biologic product play a role in the process of approval for new biosimilars. As Brewster and Singh (2019) explain, biosimilars come after the existence of a reference biologic, which might raise issues with the latter's intellectual property rights. The biosimilars can potentially affect the marketability of the reference product and its intellectual property, both of which can have far-reaching effects on the success of sales. Consequently, both FDA and EMA take the intellectual property rights of the reference products into consideration during the approval process. One of the considerations that the agencies make before approving the biosimilar product is whether it is close in its properties to the reference product, can produce the same clinical effects, and is as safe and effective as the originator biologic (Brewster & Singh,

2019). EMA (2019) specifies that the biosimilar has to have a positive benefit-risk balance – that is, its active substance must be highly similar to the reference medicine as ascertained by comparability studies. When these details have been ascertained, the product can then be declared interchangeable with the reference biologic.

The biosimilar could be similar enough to the reference biologic but not close enough to infringe on or be covered by a patent claim. Lev-Ari (2012) explains some of the components that reference product manufacturers consider in ensuring that they obtain broad patent protection for the products that they release into the market. Some of the components include safeguarding the rights to the creation of the biologic product itself, rights to the target molecules of the biologic product, and rights to the methods employed in the manufacture of the product (Lev-Ari, 2012). These diverse components then form the intellectual property rights of the reference manufacturers regarding the biologics. Some manufacturers go as far as obtaining patent rights for the potential modifications that can be done on the products.

When developing biosimilars, the manufacturers also make considerations of how to escape the patent protections and rights of the reference product manufacturers. Lev-Ari (2012) explains that their considerations in the process include examining and analyzing possible ways to escape the patent protection associated with the product that they are trying to replicate. To achieve that, they should be able to map the patent landscape of the products that they tend to create for specific markets if they are targeting the USA. They should develop a patent map for the product in the country, a requirement which also proves necessary for the EU market (Druehdahl et al., 2020). During the process of applying for approvals from the FDA or EMA, the biosimilar manufacturers should make well-informed admissions on the elements of the similar product that are equivalent to the reference product (Lev-Ari, 2012). The admissions should be carefully selected because, by USA law, the biosimilar manufacturer must also send a copy of the application to the reference product sponsor once the FDA accepts the application (McGlynn et al., 2020). Similarly, in the EU, EMA's scientific committees especially CHMP are also actively involved in scrutinizing the resourced data to produce a scientific opinion on the application and the affected patents (EMA, 2019). In correspondence, the reference product sponsor also sends a list of the intellectual property rights that the biosimilar applicant potentially infringes through the proposed new product.

In the USA, the BPCIA provides a certain amount of protection to the pioneer biologic through data exclusivity. The exclusivity usually lasts for four years under FDA standards even though new biosimilar approvals can only be done after 12 years and 10 years as per the EMA standards (Love, 2021). When the biosimilar applicant has a conceptual map of all the intellectual property rights associated with the reference product, they can be in a position to understand whether they can proceed to develop the new product by making improvements to the reference biologic or performing modifications that are not covered by the sponsor's intellectual property rights. Once the exclusivity period expires, manufacturers of biosimilars or proposed new products are free to use the information from the previously patented item to make their replacement products. Lev-Ari (2012) notes

that manufacturers of reference products address this loophole by obtaining intellectual property protection for improvements to the product.

Owing to the existence of intellectual property limitations, many biosimilars directly infringe on the rights of the reference products. Consequently, one of the legal strategies that biosimilar manufacturers who are applying for FDA or EMA approval implementation, involves the “patent dance” process, during which the biosimilar applicant and reference product sponsor engage in a series of correspondences, litigations, and settlement processes before the new product can be released into the market (McGlynn et al., 2020). The process is usually resource-intensive, time consuming, and requires adequate and in-depth planning to oversee during the approval process. Therefore, the consideration of the approach to adopt when seeking the FDA or EMA approval for biosimilars is indispensable, because it determines the duration that the applicant will take before getting the products to the market and how much financial resources it will require during the ensuing litigations should the process involve the patent dance.

Intellectual property factors also play a crucial role after the approval by FDA or EMA. According to Lev-Ari (2012), the biosimilar manufacturer must also secure the intellectual property rights associated with the developed product and any further improvements that can possibly be made on it in the future. As Love (2021) notes, the approval of a biosimilar product is likely to pave way for the development of more generic medicine options at cheaper costs than either the reference biologic or the created biosimilar. Consequently, for the manufacturer to stay profitable, there is a need for the consideration of the elements of the product that can be protected through intellectual property rights. It is critical, when securing the rights, to consider the associated patents that have already been filed by the original biologic manufacturer to avoid any further infringements (Lev-Ari, 2012). Therefore, intellectual property rights are an influential factor in the process of seeking approval from the authorities for the release of biosimilars to both the USA and EU markets.

4. IMPACTS OF THE EXPIRATION AND EXTENSION OF BIOLOGICS PATENTS

The increase in the number of expiring patents on biologic drugs is also associated with an increase in the number of applications for abbreviated biologics licenses (Figg et al., 2019). In the USA, the expiration of primary biologic drug patents is not always accompanied by the application of biosimilars. Figg et al. (2019) provide examples of drugs whose primary patents have expired but still have pending use patents that bar biosimilars from obtaining FDA or EMA approval. There are several others, however, whose expiry will open doors or have opened doors for the production of biosimilars that promise great financial incentives to the manufacturers. For instance, there are three USA patents on biologics Amevive, Lemtrada, and Rituxan that have expired. In their place, the marketability of biosimilars is estimated to be worth USA \$4.5 billion. Only two of the biosimilars for the biologic rituximab and 5 biosimilars for trastuzumab have been licensed by the FDA for commercial use. Two others had pending approvals with the FDA at the time of the publication of the GaBI Journal (2020) article.

The biosimilars market is expected to soar in terms of sales revenue even as biologics expire. The Pharmaceutical Technology (2019) reported that the expiry of “blockbuster” biologics, the growing burden of chronic diseases, and the cost-cutting initiatives by the government are some of the leading factors behind the increasing popularity of biosimilars. For instance, in 2018, the antibody drug – Humira – lost its patent exclusivity in the EU, and the occurrence prompted the increase in the number of biosimilars attempting to penetrate the USA \$19 billion market share that the company had held in the continent (Pharmaceutical Technology, 2019). The opportunity that such expirations have opened up has also seen governments moving to sign deals with companies offering lower-cost alternatives with the intention of reducing healthcare spending. Pharmaceutical Technology (2019) highlighted the move by the UK National Health Service (NHS) to negotiate deals with five manufacturers for the development of low-cost alternatives to Humira with an aim of saving up to USA \$395 million on the drug.

The GaBI Journal (2020) reports that the opportunity for biosimilars in the US is highly lucrative. There are approximately 71 biologic patents that are set to expire by the year 2023, with the value in sales that the opportunity offers for competitors who would manufacture and sell biosimilars being USA \$55 billion (GaBI Journal Editor, 2020).

For instance, biosimilar manufacturers stand a chance to reap USA \$20 billion in sales after the patents on Humira, Kadcyra, Lumizyme, and Stelara expire. Such an opportunity is also available for the EU markets. As Schiestl et al. (2017) report, the expiry of data protections and patents on original biotherapeutics paved the way for the development of biosimilars which subsequently gained approvals from the EMA and penetrated the market. The EU Directive 2004/27/EC underwent a revision in 2004, after which it allowed for the full development of biosimilars before the patent of a reference product manufacturer expires (Schiestl et al., 2017). Consequently, manufacturers develop biosimilars as soon as the expiry of a patent for a biologic draws close. The extension of patents after the expiry of the basic patents is difficult to achieve. Moorkens et al. (2020) made this assertion after conducting a study of whether patents on specific biologics had become a barrier to the biosimilar market entry. The authors noted that with the expiry of the patents for high-selling biological medicines came the growth in the opportunities for non-innovator versions of the medicines, with biosimilars being the leading beneficiaries (Moorkens et al., 2020). Some patent holders make applications to extend the protection for the active ingredients in their pharmaceutical products once the basic patent expires. However, Moorkens et al. (2020) note that this is not an extension of the patent, but the national supplementary protection certificates (SPCs) can confer to the registered medicines the same rights as the initial patent offered. However, with the EU Directive 2004/27/EC allowing for the full development of biosimilars before the patent expires, extensions granted by the EMA are uncommon for biologics (Schiestl et al., 2017). Moorkens et al. (2020) also note that additional patents after expiry are difficult to obtain.

From the study findings, the trend is that the basic patents on the biologics – those that cover the rights to the manufacture of the product and the trade secrets – offered protection against the entry of competitive biosimilars into the market (Moorkens et al., 2020). Any additional patents do not offer adequate protection

against the entry of competitive biosimilars. The major hurdle that the extension requests present is the protracted delays in the launch of the product into the market as litigations go on for long periods (Moorkens et al., 2020). The authors also note that many biosimilar applicants win litigation cases against the reference product sponsors and successfully launch their products into the market. The biosimilars themselves are adequately protected when the manufacturers file new patents protecting them and the production procedures. The situation is relatively similar to the environment in the USA, Mahn (2017) argues that the BPCIA's declaration of the possibility of extending patent periods for the active ingredients in biologics introduces ambiguities to the legislation that provides little protection to biologics patent holders for the extension of their patents. Consequently, there is little that the reference biologic product sponsors can do to prolong the patents that they have for their products, which gives room for the biosimilar manufacturers to launch new products into the market after the expiry of the related base product. Rees (2020) reports that the expiry of biologics patents is expected to have a positive impact on the country's pharmaceutical industry.

Kang and Knezevic (2018) cite the example of trastuzumab, a breast cancer biologic that expired in the EU in 2014 and expired in June 2019 in the USA. At the time of publishing the report, there were already several biosimilars to trastuzumab that were in circulation in the EU countries and were making applications for approval in the USA. The result was an expected availability of biotherapeutics at affordable prices in the USA and the promotion of the diversity of treatment options that patients can choose from (Kang & Knezevic, 2018). With the extension of biologic patents shrouded in legal doubts, there are opportunities for biosimilar manufacturers to produce new products, obtain approval from the FDA, and launch them to the USA market once the patents for the reference medicines expire.

5. EFFECTS OF LAWSUITS FROM BIOLOGICS COMPANIES AND OTHER BARRIERS

The agencies in the USA and EU have created abbreviated pathways for the approval of biosimilars. The aim of the implementation of abbreviated pathways was to enhance competition and lower spending on the biologics once the originators lose their exclusivity to the market – especially after their patents expire (Druehdahl et al., 2020). However, the aims have not particularly been met in either region. As the GaBI Journal (2020), the FDA had approved 26 biosimilars for the USA by the end of 2019. The biosimilars were approved for nine originator biologics, but only 14 of them were launched in 2020 (Druehdahl et al., 2020). In the EU, EMA approved 64 biosimilars for 16 biologics by May 2020, with the ensuing price reductions ranging from 3% to 30% depending on the therapy (Druehdahl et al., 2020). Consequently, biosimilars have not successfully achieved the aims for which the approval pathways were eased. This fact points to the existence of various barriers to the introduction of the products to the market and their successful retail at affordable prices.

One of the barriers to the introduction of new biosimilars is the legislative framework surrounding the existence of originator patents. Druehdahl et al. (2020) found out the existence of originator patents that block the sharing of trade secrets on biologics and the execution of certain scientific processes required for the development of biosimilars. As Murthy (2013) indicates, product patents, which could expire and open the landscape for

biosimilar manufacturers, are often accompanied by patents on the process, formulation, method of use, dosing regimen, and devices, all of which cover various aspects of the biosimilar development or use process.

The existence of such patents can delay the introduction of the new biosimilar to the market even when the product patent for the originator biological has expired (Murthy, 2013). Thus, biosimilar manufacturers run the risk of facing litigation for breaching the intellectual property rights and patents filed by originator manufacturers. Furthermore, Druedahl et al. (2020) report that the companies face risks as they are unable to map the patent landscape in the USA and uncover similar patents in the EU, which exposes them to the probability of breaching the rights of the patent holders and being legally liable for lawsuits.

The biggest barrier remains the litigation involving biologics manufacturers and the creators of new biosimilars. McGlynn et al. (2020) outline how a “patent dance” procedure – when a biosimilar manufacturer decides to clear the patent rights of a reference patent sponsor during the approval process or before product launch. Such cases present the classical example of how lawsuits can impede the introduction of biosimilars. In the USA, the FDA approval process requires the product sponsor for the biologic to a license application after patenting the product (McGlynn et al., 2020). A biosimilar applicant who produces and tests a product similar to the reference biologic also files a Biologics License Application (BLA) with the FDA to seek approval. This filing should occur at least four years after the reference product is approved. The applicant must demonstrate that the product is similar to the approved biological, after which the FDA accepts it for review.

BPCIA then outlines the patent dance process that ensues – the biosimilar applicant gives the reference patent sponsor the FDA application form, to which the sponsor replies with a patent list, and the applicant responds with the patent list and the contentions (McGlynn et al., 2020). The sponsor also presents its contentions, after which the parties engage in negotiations on the patent list and the sponsor files a complaint. The first wave of the BPCIA litigation then commences. The FDA can approve the biosimilar application during or after the first wave of litigation, to which the applicant issues a 180-day pre-market notice. A second wave of BPCIA litigation with the reference patent sponsor can ensue, involving the request for an injunction against the manufacture or sale of the biosimilar. If no injunction is filed or the court rules to bar the preliminary injunction, the biosimilar can be produced and released into the market even when litigation is ongoing (McGlynn et al., 2020). Otherwise, depending on the court decision, there might be further delays in the product launch during the second wave of litigation.

The reference sponsor’s product patent might expire during or after the second wave of litigation. The McGlynn et al. (2020) note, however, that the biosimilar applicant might still be liable for pre-launch patent infringement activities that it performed when the patent was still in force, which could further lead to delays in the launch of the product in the market. The clearest pathway to the successful launch is when the two waves of litigation are resolved or when the parties arrive at a settlement agreement dictating when the biosimilar can enter the market (McGlynn et al., 2020). A good example is the unsuccessful patent challenges against Enbrel, with the numerous Humira patents asserted by AbbVie against biosimilar manufacturers driving the latter to settle on

release dates for biosimilars in the year 2023. The protracted litigation processes can last several years, and even then, there will be uncertainties regarding the competitiveness of the biosimilars.

There are various examples where long periods of litigation involving biosimilars have delayed their approval or release into the market. Rees (2020) highlights the fact that before the year 2019, few biosimilars received FDA approval, after which they faced stiff legal battles that delayed their release into the market. In 2019, the agency made a remarkable turnaround after approving six oncology biosimilars by companies such as Merck, Pfizer, and Amgen, which went ahead to launch into the market in the following months. Rees (2020) also explains that the low US market penetration by biosimilars in immunology was majorly due to the stiff litigation challenges that the manufacturers were encountering in American courts. The case of AbbVie's adalimumab biosimilar's scheduled launch in the USA market in 2023 is a testament to this fact, considering that the company has made inroads in the EU market with various adalimumab biosimilars that were launched in 2019 (Rees, 2020). Thus, the litigation process in the USA can introduce delays to biosimilar launches by several months and years.

In the EU, a similar structure for challenging the reference biological product (RBP) patents in existence for the creation of a new biosimilar. The European Patent Office (EPO) allows biosimilar manufacturers to challenge the key patents of RBPs through a single forum (Malkin, 2015). The outcomes of such challenges could be the rejection of the opposition and maintenance of the patent, the amendment of the patent with new specifications, or the revocation of the patent. The decisions can be appealed within two months, with the appellate process occurring for a median duration of three years. The litigation process – including the initial opposition and appeals – introduces delays of several months or years to the manufacture and release of the new biosimilar. For instance, there are manufacturers who filed oppositions against biologics such as epoetin, filgrastim, infliximab, insulin glargine, and somatropin, with the pending cases preventing the launch of biosimilars into the European markets at the time of the publication of the article (Malkin, 2015). However, the effects of litigation on the release schedule are not as pronounced in the EU as is the case with the USA.

Another barrier to the fast launch of biosimilars to the market is systemic, with the limitation occurring from the principles that the regulatory agencies have put in place. Regardless of the outcomes of the litigation process, the release of new biosimilars will take at least a decade after the launch of the reference biologic. Love (2021) mentions the fact that the EMA can only approve a biosimilar after 10 years after approving the reference biologic. In the USA, the FDA holds off the approvals of new biosimilars for 12 years after giving its approval for the reference biologic (Love, 2021). McGlynn et al. (2020) emphasize this fact by mentioning that between the FDA's approval of the biologics license application, 12 years have to elapse before it gives approval to the biosimilar applicant's product.

6. POLICY RECOMMENDATIONS

The United States lagged behind Europe initially in instituting a timesaving biosimilar process, however after instituting the 351(k) of the Public Health Service Act (PHS Act) licensure pathway, it permitted biosimilar

products to be licensed much faster. Despite the implementation of the quicker process to bring biosimilars to the market, the USA has lagged in biosimilar market development. Data through early 2019 reflects seven of seventeen biosimilars of four biologics were commercially available (Yazdany J, 2018). Ten approved biosimilars through this period were unavailable.

Biologic producers can hinder biosimilars market introduction through legal litigation after FDA approval (Cottler M, et al., 2018). Patent litigation defers entry as a result of settling a patent dispute on infringed patents protecting the originator biologics (Hertfordshire, England: Mylan., 2017).

Patent thicket, refers to a strategy of creating a wall of strong patents to protect properties (loftus, P., 2019). In 2016, AbbVie's patent on Adalimumab expired and was permitted successions of patent protections that included the manufacturing process and construction of the drug (loftus, P.,2019). The patent applications were filed by AbbVie after Adalimumab was on the market and subsequently in 2016 when the patent expired. Through the use of patent thicket, AbbVie litigated the manufacturers of Adalimumab biosimilars, including Amgen, Boehringer Ingelheim, Mylan, Pfizer, Samsung Bioepis, and Sandoz, for patent infringement. Manufacturers of biosimilars settled in terms that included the implementation of licensing contracts where the biosimilar manufacturers delay entry of the drugs and pay AbbVie licensing fees after biosimilars reach the market (North Chicago, IL: AbbVie, 2018). Because there are no alternatives for Adalimumab continues to grasp its full market. Without competition, AbbVie is free to continue to raise prices. Delays of biosimilars being available in the market adds to the cost of medications to tax payers and patients (Schumock GT., et al., 2017). In contrast, because of the European markets have stronger consumer protection for biosimilars in having state sponsored price controls, prices for drugs including Adalimumab are less expensive. In 2019, The USA senate introduced a bill that would have addressed the problem of patent thickets but failed due to the drug companies' aggressive exertions on the senate and congress. US drug companies are also allowed to lack transparency in their pricing. This results in consumers not being able to know what prices they will pay for medications nor whether they could select less expensive alternatives. The USA needs to address patent thicket to avert increasingly unjustifiable price increases by drug companies.

Further, in contrast to the European EMA, the USA FDA requires that biosimilars demonstrate that they are interchangeable with the original biologic prior to allowing subscriptions by pharmacies to have automatic replacements. The interchange replacement between biologics and biosimilars is a decision best deferred to prescribing physicians.

7. CONCLUSIONS

This paper examined the significant structural differences that contrast Europe and the United states in biosimilars approvals. Regulatory processes and market subtleties create a divergence of the markets. Biosimilars have not achieved intended potential of market competition that leads to high marketability and price reductions; biosimilars have acquired only small market percentages of their biologic associations. Biosimilars generally have been introduced at slight discounts from their base biologic associations and have

attained single digit fractions of the biologic market. Making the introduction of biosimilars more difficult, biologic producers have engaged in strategies that delay the market application of approved biosimilars.

The overall conclusion is that there are various examples from Europe that the USA could consider embracing that would lead to lower biosimilar and biologics pricing. Particularly, policy changes aimed to encourage the healthcare industry to help educate the public to address false notions of biosimilar's effectiveness and safety as well as increasing incentives for prescriptions to include biosimilars in lieu of biologics to aid in equalizing market pricing.

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