GENERICS AND BIOSIMILARS INITIATIVE JOURNAL
Building trust in cost-effective treatments

The European framework for intellectual property rights for biological medicines

Generics and Biosimilars Initiative Journal (GaBI Journal). 2021;10(4):172-83
DOI: 10.5639/gabij.2021.1004.022

Published in: Volume 10 / Year 2021 / Issue 4
Category: Review Article
Page: 172-83
Visits: 1913 total, 10 today

Keywords: biological medicines, European intellectual property rights, market access, pricing, R & D

Author byline as per print journal:*Josette Sciberras, MBA, MA Bioethics, BPharm (Hons); Raymond Zammit, SThD; Patricia Vella Bonanno, PhD*

Introduction: The Pharmaceutical Strategy for Europe (2020) proposes actions related to intellectual property (IP) rights as a means of ensuring patients' access to medicines. This review aims to describe and discuss the European IP framework and its impact on accessibility of biological medicines and makes some recommendations.
Methods: A non-systematic literature review on IP for biological medicines was conducted. Data on authorizations and patent and exclusivity expiry dates of biological medicines obtained from the European Medicines Agency's (EMA) website and literature was analysed quantitatively and qualitatively.
Results: The analysis showed that as at end July 2021, 1,238 medicines were authorized in Europe, of which 332 (26.8%) were biological medicines. There were only 55 biosimilars for 17 unique biologicals. There is an increasing trend in biological authorizations but significant delays in submission of applications for marketing authorization of biosimilars, with no significant differences in the time for assessment for marketing authorization between originator biologicals and biosimilars. For some of the more recent biosimilars, applications for authorization were submitted prior to patent and exclusivity expiry. COVID vaccines confirmed the impact of knowledge transfer on accessibility, especially when linked to joint procurement.
Discussion: IP protects originator products and impacts the development of biosimilars. Strategies to improve competition in the EU biological market are discussed. Pricing policies alone do not increase biosimilar uptake since patients are switched to second generation products. Evergreening strategies might be abusing the IP framework, and together with trade secrets and disproportionate prices compared to R & D and manufacturing costs lead to an imbalance between market access and innovation.
Conclusion: The European Pharmaceutical Strategy should focus on IP initiatives that support earlier authorization of biosimilars of new biologicals. Recommendations include knowledge sharing, simplification of the regulatory framework and transparency of prices and R & D costs.

Submitted: *21 April 2021;* ***Revised:*** *4 September 2021;* ***Accepted:*** *8 September 2021;* ***Published online first:*** *20 September 2021*

Introduction

The EU biological medicines market

It is estimated that 25% of all new medicines developed are biologicals [1]. In 2018, the global biological market was worth approximately US$276 billion with 10 blockbuster drugs being biologicals, which increased from 3 such drugs in 2003 [2]. Table 1 shows the net sales of the top selling biologicals as reported by Pharmaceutical Technology [3]. In September 2019, monoclonal antibodies (mAbs) featured in the top 10-selling blockbuster prescription medicines globally by revenue, with adalimumab (Humira®) being the number one with US$19.9 billion sales and accounting for 7% of all global sales on the market despite the launch of biosimilars [3].

About GaBI Journal
- Editorial Objectives
- Editorial Sections
- Governance
- Editorial Board
- International Editorial Advisory Board
- Peer Review Policy
- Editorial Calendar
- Indexation

Current Issue
Previous Issues
Forthcoming Issue
Information for Authors
- Call for Papers
- Instructions for Authors
- Types of Paper
- Manuscript Submission
- Submit Letters to the Editor
- Article Processing Charges
- Copyright
- Fast Track
- Author Resources

How To
- Submit a Manuscript
- Obtain Permissions
- Order Reprints
- Sponsor a Supplement
- Subscribe

Advertise
- General Introduction
- Circulation Profile
- Features
- Benefits
- Material Requirements

Contact
Related Sites

Table 1: Top-selling biologicals by net sales and patent expiry

Position	Brand name	INN	Net sales (US$ billions)*	Patent expiry**
1	Humira	Adalimumab	19.9	October 2018
2	Eliquis	Apixaban	9.8	May 2026
3	Revlimid	Lenalidomide	9.7	July 2022
4	Keytruda	Pembrolizumab	7.1	June 2028
5	Enbrel	Etanercept	7.1	August 2015
6	Herceptin	Trastuzumab	7.0	July 2014
7	Avastin	Bevacizumab	6.9	January 2022
8	Eylea	Aflibercept	6.7	May 2020
9	Opdivo	Nivolumab	6.7	May 2026

*Pharmaceutical Technology [3].
**Data on patent expiry collated from [2].

INN: International Nonproprietary Name.

The prices of biological medicines range in the thousands of Euros, making them unaffordable to some patients and some healthcare systems [4]. Innovation is considered to be the major driver of healthcare costs [5]. Biological medicines are the key drivers for the increase in pharmaceutical expenditure for the treatment of cancers, autoimmune disorders and diabetes [6]. These chronic diseases are responsible for the economic burden of disease or the 'cost-of-illness' both through direct costs (the cost of medicines) and indirect costs (the cost as a consequence of the disease) [7]. The problem of affordability for low-income countries and financial sustainability of healthcare systems, even in high-income countries, are a priority on the agenda of policymakers [6].

The European Commission acknowledges that health systems and patients have difficulty bearing the cost of medicines. In November 2020, it proposed a Pharmaceutical Strategy with one of the aims to ensure access to affordable medicines for patients whilst supporting competitiveness, innovation and sustainability of the EU's pharmaceutical industry and the development of high quality, safe and effective medicines [8]. At its June 2021 meeting, the Council of the European Union approved the proposal for the revision of the regulatory framework for intellectual property mechanisms and the pharmaceutical legislation related to market competition to improve access to biosimilars so as to increase competition whilst protecting innovation [9].

Scope

The EU defines a biological medicinal product as 'a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterization and the determination of its quality a combination of physicochemical and biological testing, together with the production process and its control' [10]. For the purpose of this paper the following shall be considered as biological medicinal products: immunological medicinal products, medicinal products derived from human blood and human plasma, advanced therapy medicinal products, vaccines, allergens, gene therapy and biotechnology-derived products (recombinant medicinal products).

Aim and objectives

The aim of this study is to describe and discuss the EU intellectual property (IP) framework and its impact on access to biological medicines in order to improve their accessibility to patients. The first objective of this study is to discuss the IP system applicable to biological medicines in Europe. The second objective is to identify their impact on access to biological medicines through a quantitative and qualitative evaluation of biological authorizations by the European Medicine Authority (EMA) (1995 to July 2021). The third objective is to provide recommendations for improvement in order to increase access to biological medicines.

Methodology

A non-systematic literature review was performed through Google search on the following keywords: intellectual property rights, patent, R & D, biological medicines, pricing of medicines in Europe and accessibility. The list of medicines authorized until 31 July 2021 was retrieved from the EMA website which was last accessed on 1 August 2021 [11]. The authorized medicines were grouped as biological or non-biological based on the EMA definition [10] and the biosimilars were identified from the data downloaded. Data on first time authorizations was retrieved. This allowed the authors to measure the time between authorization of the biosimilar and that of its reference product. Further analysis was performed to identify the monoclonal antibodies authorized in Europe. The date of entry into force of biosimilar guidelines and product specific guidelines were retrieved from the EMA website. The patent and exclusivity expiry dates for originator biologicals for which a biosimilar is available were identified. A sub-analysis was performed on all biologicals authorized between 2006 and July 2021 with the aim to identify any differences in time for assessment for marketing authorization by EMA between originator and biosimilars.

Results

Review of the EU intellectual property protection framework for biological medicines

The European IP framework for biological medicines covers trade secrets, patents and European incentives to the pharmaceutical industry, including Supplementary and Protection Certificate, data, and market exclusivity, among others.

Trade secrets

It is claimed that trade secrets for biologicals contribute to the high cost of US$100–US$200 million for bringing a biosimilar to the market when compared to that of US$1–US$5 million for a generic medicine [12]. In the EU, trade secrets (referring to undisclosed know-how and business information) are protected at both European and national levels. EU Regulation 2309/93 provides protection against commercialization of trade secrets contained in applications for medicinal products [13]. On a global level, IP rights are regulated by the World Trade Organization (WTO) for its member countries through the setting up of Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement, to which the European Community (EC) is also a party. Directive (EU) 2016/943 on trade secrets in Europe, which came into force in June 2016, is aimed at achieving harmonization for protecting and defending trade secrets across the EU [14]. Companies resort to trade secrets over and above patents so as to protect certain IP rights perpetually [15]. Data information resulting from research, clinical trial data and manufacturing processes of biologicals, proprietary biological databases and cell-lines are examples of data considered to be trade secrets [15]. In order to create a copy of the original biological, the originator cell line would be necessary for the competitive applicants [16]. This creates a 'knowledge gap' between the originator company and the competitive applicant [16]. The 'knowledge gap' could be closed or eliminated through disclosure of information. Dzintars Gotham (2018) proposed that prior to patent expiry, the originator company provides access to cell line and detailed description of the manufacturing process, termed as cell line access (CLA), where the product produced is referred to as a CLA biological [12]. A similar proposal was made by Knowledge Ecology International and Price & Rai (2017) who had proposed incentives to encourage disclosure of company secrets related to the manufacturing processes [12]. Gotham proposed the depositing of a living vial of the cell line to the regulatory authority on regulatory approval [12]. Lisa Diependaele and colleagues recommended some form of compensation to originator companies granting CLA through remuneration in terms of a contractual agreement with the competitor [17]. Yaniv Heled, however, claimed that developers should have access to whatever knowledge and material of the originator that was needed to create a copy at the expiration of the data exclusivity period. Heled argued that sample depositing and sharing requirements have already been incorporated in the US patent as well as Food and Drug law [16]. Though EU law already allows for sample depositing of cell lines, for example, for advanced therapeutic medicinal products and for patenting, this is not yet the case with respect to all biologicals. If an identical cell line and manufacturing process are used, the differences in the quality, efficacy and safety profile between the CLA biological and the originator are considered as minor and phase III comparability clinical studies may not be required by the regulatory authorities. *In vitro* analytical results would suffice to demonstrate clinical equivalence of the CLA biological [16]. The originator company would still benefit from IP rights enjoyed as per legislation, but other companies would market the CLA biological immediately on expiry of the exclusivity protection, resulting in greater price reductions.

Patent system

Patent law dates back to the Age of Enlightenment and is aimed at rewarding the inventor for disclosing one's invention to make it freely available for the benefit of society [18]. Patents were originally introduced in biotechnology by farmers over a hundred years ago [19]. They may cover 'the active ingredient, formulations, methods of medical treatment, method of manufacturing and chemical intermediaries' [20].

In Europe, prior to 1994, patents were regulated at national level. Since then, they are regulated by the European Patent Office (EPO) which mandates that medicinal products be covered "by patent protection for a minimum of twenty years from the filing date of a patent application for any pharmaceutical product or process that fulfils the criteria of novelty, inventiveness, and usefulness" [21]. As from the year 2000, an inventor in the EU may choose to apply for a national patent or with the EPO, in which case the inventor should indicate the Contracting State this would apply to within the EU [20]. From a patent period of 20 years, generally 12–13 years are required for a new active substance to finally reach the market, with only eight years of patent protection remaining, which is not considered sufficient to obtain a return on investment [22].

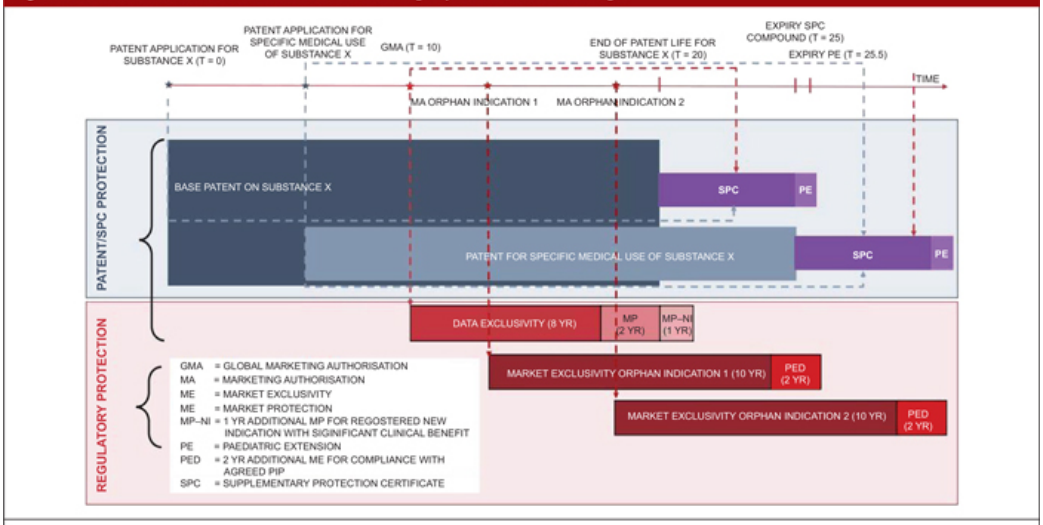
Originator companies aim to retain monopoly status by setting high barriers to entry for competitors in order to recoup investment costs, regain the R & D costs and cover the high risk of failure [20]. The EC legislator argued that "without effective means of enforcing intellectual property rights, innovation and creativity are discouraged and investment diminished" [20].

The exorbitant prices of the blockbusters, especially mAbs, are presenting accessibility problems also in developed countries, such that European Governments considered using the 2001 Doha Declaration through the use of the compulsory licencing for biologicals [23]. WTO members declared that TRIPS "should be implemented in a manner supportive of WTO members' right to protect public health and, in particular to promote access to medicines for all," with the aim of protecting the health of populations in developing countries [21]. The compulsory licence "allows a patent to be used without the consent of the patent holder for a reasonable royalty payment" [24]. Governments could use compulsory licence allowing production or importation or procurement of generic or biosimilar medicines where the price of the originator medicine is considered to be unaffordable [24]. For medicinal products which are authorized through the EU centralized procedure, the EU data exclusivity directive (known as the '8+2+1' regime) supersedes a compulsory licence, even if such licence was issued [24]. The European Parliament called on the Commission and Member States to make use of flexibilities under the WTO TRIPS agreement such as compulsory licensing and parallel importation and to coordinate and clarify their use where necessary [25]. The process is a complex one and these flexibilities are legally challenging.

European IP incentives for the pharmaceutical industry

European IP incentives were introduced with the aim of protecting innovation to newer therapies, whilst keeping a balance to provide accessibility through more affordable generic or biosimilar medicines [26]. The various regulatory mechanisms include: the Supplementary Protection Certificate (SPC), data and market exclusivity, Paediatric Use Marketing Authorisation (PUMA) and marketing exclusivity for orphan drugs. The relationship between the various mechanisms is illustrated in Figure 1 [27]. This figure refers to "global marketing authorisation" which contains the initial authorization and all variations, extensions, additional strengths, pharmaceutical forms and administration routes for a specific active substance authorized within the EU [27]. It does not cover further medical indications of the same active substance, which would generate a new period of data exclusivity and market protection [27].

Figure 1: Relations between the various Intellectual Property mechanisms in Europe



Blue part – patency period and its extension through the SPC; for a basic patent of Substance X, it is extended to 25 years; extended by 6 months for paediatric indications; for a specific medical use of Substance X, patency and SPC period commence at the date of patent application for that medical use.
Red part – data exclusivity ("8+2+1" regime); for orphan medicines, market exclusivity rights of maximum of 10 years, extended by two years for paediatrics; for a new indication of the orphan medicine, the market exclusivity right commences at the time of market authorisation for the new indication].
De Jongh, Thyra, Alfred Radauer, Sven Bostyn, Joost Poort. Effects of supplementary protection mechanisms for pharmaceutical products. The Netherlands: Technopolis Group Final report, May 2018 [27].

Supplementary Protection Certificate (SPC)

As per Regulation (EC) 469/2009 [28], at the end of the patent life, a maximum five-year extension may be granted to a patent right. The Supplementary Protection Certificate (SPC) may be extended by a further six months, referred to as a Paediatric Extension (PE) if studies (referred to as the Paediatric Investigation Plan (PIP)) are performed to support paediatric indications, so as to ensure that children also benefit from innovative therapy. Multiple SPCs exist for the same product across Europe as SPCs are granted by the national patent office. Different interpretations of the regulation by national patent offices and courts resulted in inconsistencies across Member States which led to a ruling by the Court of Justice by the European Union (CJEU) that concluded that there was the risk that the SPC mechanism was being used to extend patent protection that goes against the spirit of the same regulation which should consider primarily the interest of public health [29]. A 2019 waiver of the SPC allowed EU-based generic and biosimilar companies to manufacture SPC-protected medicines but only for export to non-EU countries where protection of the SPC expired or is non-existent or for stockpiling during the final 6 months of an SPC before entry into the EU market [29]. It was therefore argued that the changes made to the SPC manufacturing waiver do not address the issue of affordability and accessibility of medicines in Europe [4].

Data and market exclusivity

Referred to as the '8+2+1' regime, this harmonizes the EU period of protection of data for innovative products, starting at the point of 'global marketing authorization'. As shown in Figure 1, this regime provides eight years of data protection, during which the data of the reference product cannot be used by other manufacturing companies to obtain marketing approval for the generic product. An additional two years of market exclusivity are granted during which regulatory authorities cannot grant a marketing authorization to the generic product. An additional one year is granted for new therapeutic indications, such that an originator product may benefit from a maximum of 11 years data exclusivity [30]. An investigation that was commissioned by the government of The Netherlands to evaluate the cumulative costs of the supplementary protections to the Dutch healthcare system for three drugs could not confirm that innovation was improved through the '8+2+1' regime, and subsequently called for further investigation [25].

Paediatric-Use Marketing Authorisation regulation (PUMA)

An additional data exclusivity of 8 years and market exclusivity of 10 years from the date of marketing authorization may be granted for those medicinal products authorized exclusively for children, and which are not protected by an SPC or SPC qualifying patent. Its aim is to drive innovation in medicines for children, especially in oncology and neonatology, which is still lacking behind.

Marketing exclusivity for orphan drugs

Supplementary marketing exclusivity for orphan medicines is granted at the point of marketing authorization for each specific indication. This is aimed to protect innovation of medicines intended for rare diseases or where the medicine is unlikely to generate sufficient profit due to very high R & D costs. As illustrated in Figure 1, on granting of a marketing authorization for a specific indication, an orphan medicine may benefit from up to an additional ten years of market exclusivity. A further eight years of market exclusivity are granted at the point of the market authorization of the second indication, with the possibility of another two years for a paediatric indication. Research tends to be focused on the development of 'blockbuster' drugs which render a high return on investment, resulting in the disproportionate allocation of resources on some diseases at the expense of leaving others untreated [31]. The European Parliament recommended reviewing the prioritization system of unmet medical needs and the definition of orphan drug designation by revising the rare disease register, whilst calling on the Commission to revise the requirements of public funded research in this regard [25].

Analysis of the impact of the EU IP framework for biological medicines

Impact on authorizations of biologicals in Europe

An analysis of medicines authorized by EMA showed that as of 31 July 2021, 1,238 medicines are authorized, 332 (26.8%) of which are biological products for 277 biological active substances, see Table 2. Figure 2 shows an increasing trend in authorizations of biologicals in Europe since 1995, starting from an average of six per year for the period (1995–2001) to an average of 28 per year for the period (2016–July 2021), which peaked to 41 in 2018, 13 of which were biosimilars. Figure 3 shows an increase in authorization of monoclonal antibodies in recent years. Table 2 shows that there are 55 biosimilars (excluding products marketed under different brand name) authorized for only 17 of biological active substances, see Table 3. Figure 2 shows that notwithstanding the 2004/27 Directive, there were few biosimilars approved between 2006 and 2016 (a period of 10 years), and though quite a number of biosimilars were approved in 2017 and 2018, the numbers decreased in the following years.

Table 2: Biological medicines authorized in Europe by category (1995–July 2021)

Year	Total biologicals	Originator biologicals	Biosimilars	Total monoclonal antibody	Originator mAbs	Biosimilar mAbs
1995	2	2	0	0	0	0
1996	5	5	0	0	0	0
1997	6	6	0	0	0	0
1998	3	3	0	2	2	0
1999	6	6	0	2	2	0
2000	10	10	0	1	1	0
2001	10	10	0	0	0	0
2002	11	11	0	0	0	0
2003	3	3	0	1	1	0
2004	7	7	0	2	2	0
2005	3	3	0	2	2	0
2006	10	9	1	1	1	0
2007	12	10	2	3	3	0
2008	5	4	1	0	0	0
2009	18	17	1	5	5	0
2010	9	8	1	2	2	0
2011	6	6	0	3	3	0
2012	5	5	0	1	1	0
2013	18	15	3	4	3	1
2014	14	11	3	4	4	0
2015	18	18	0	8	8	0
2016	18	15	3	5	4	1
2017	31	21	10	13	7	6
2018	41	28	13	20	12	8
2019	17	13	4	7	5	2
2020	28	19	9	5	0	5
Jun-Jul 2021	16	12	4	4	1	3
	332	277	55	95	69	26

Data collated from [11].

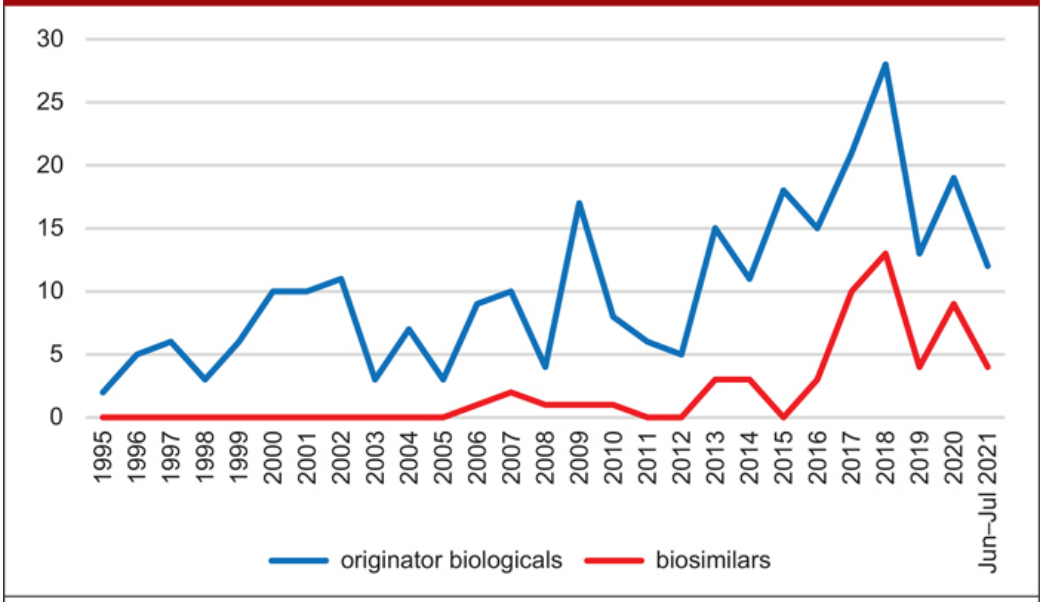
Table 3: Biological active substances with available biosimilars, and relevant data related to patents and marketing authorization (1995–31 July 2021)

Active substance	Originator first authorization date*	Patent and exclusivity expiry in the EU**	Biosimilar first submission date*	Gap between originator authorization date and biosimilar submission date (years)	Gap between patent expiry and biosimilar submission date (years)	Biosimilar first authorization date*	No. of years from first authorized originator biological	Date of coming into force of the specific biosimilar guideline***	No. of biosimilars	mAb (Y/N)
Adalimumab	07/09/2003	01/10/2018	03/12/2015	12.25	-2.83	20/03/2017	13.5	mAbs–01 Dec 2012	7	Y
Bevacizumab	11/01/2005	22/01/2022	01/12/2016	11.90	-5.15	14/01/2018	13.0	mAbs–01 Dec 2012	6	Y
Enoxaparin	≠	04/07/2005	27/05/2015	n/a	n/a	14/09/2016	n/a	LMWH–01 Jun 2017	1	N
Epoetin alfa	01/06/1989	01/06/2004	09/03/2006	16.78	1.77	26/08/2007	15.0	Erythropoietin–01 Oct 2010	1	N
Epoetin zeta	≠	Expired	28/06/2006	n/a	n/a	17/12/2007	n/a	Erythropoietin–01 Oct 2010	1	N
Etanercept	01/02/2000	01/08/2015	03/12/2014	14.85	-0.66	12/01/2016	16.0	mAbs–01 Dec 2012	3	N
Filgrastim	≠	28/06/2005	29/01/2007	n/a	1.59	14/09/2008	n/a	Recombinant GSF–01 Jun 2006	5	N
Follitropin alpha	19/10/1995	01/07/2005	28/02/2012	16.37	6.67	26/09/2013	18.0	Recombinant FSH–01 Sep 2013	2	N
Infliximab	12/08/1999	01/02/2015	01/03/2012	12.56	-2.92	08/09/2013	14.1	mAbs–01 Dec 2012	3	Y
Insulin aspart	06/09/1999	03/07/2005	29/05/2019	19.74	13.91	25/06/2020	20.8	Insulins–01 Sep 2015	2	N

Insulin glargine	08/06/2000	2014	03/06/2013	12.99	13.50	08/09/2014	14.3	Insulins–01 Sep 2015	2	N
Insulin lispro	31/07/2001	01/05/2013	07/09/2016	15.11	3.36	17/07/2017	16.0	Insulins–01 Sep 2015	1	N
Pegfilgrastim	21/08/2002	21/08/2017	27/04/2017	14.69	-0.32	20/09/2018	16.1	Recombinant GSF–01 Jun 2006	7	N
Rituximab	01/06/1998	12/11/2013	19/10/2015	17.39	1.93	16/02/2017	18.7	mAbs–01 Dec2012	4	Y
Somatropin	14/02/2001	Expired	01/07/2004	3.38	expired	11/04/2006	5.2	General–01 Jun 2006	1	N
Teriparatide	09/06/2003	01/08/2019	27/11/2015	12.48	-3.68	03/01/2017	13.6	Biotechnologically derived active proteins Revision 1–01 Jul 2015	3	N
Trastuzumab	27/08/2000	28/07/2014	30/08/2016	16.02	2.09	14/11/2017	17.2	mAbs–01 Dec 2012	6	Y

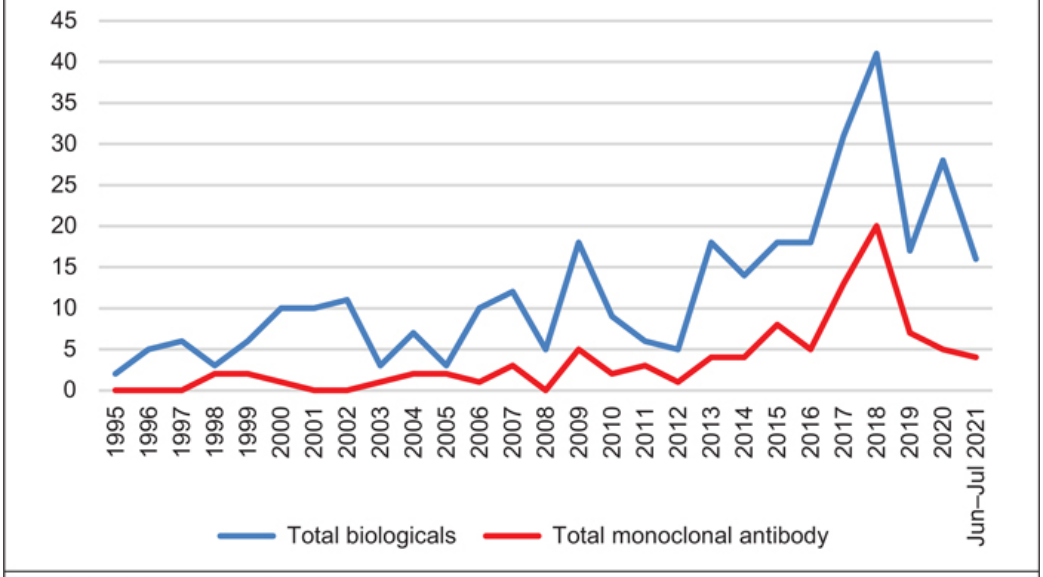
#Originator biological had been authorized through national authorization, the only form of authorization before 1995.
*Data collated from [11].
**Data collated from [2].
***Data collated from [50].

Figure 2: Trends in numbers of biological and biosimilar medicinal products authorized on the market in Europe (1995–July 2021)



Data from Table 2, collated from [11].

Figure 3: Trends of monoclonal antibodies compared to biologicals approvals (1995–31 July 2021)



Data from Table 2, collated from [11].

The results in Table 3 show that there is a significant delay in the submission of applications for marketing authorization of biosimilar products compared to first date of authorization of originator biological (11.9 to 19.74 years), with the exception of somatropin. Table 3 shows that for

six newer biologicals, the biosimilar application for authorization was submitted prior to the expiry of patent and exclusivity of the originator biological.

The results of the sub-analysis on the data between 2006 and July 2021 show that a total of 254 biologicals were authorized during this period, of which 199 were originator biologicals. The mean time for assessment of marketing authorization was 1.19 years; maximum 4.60 years and minimum 0.05 years. A total of 55 biosimilars were authorized during the same period with a mean time for authorization of 1.20 years; maximum 2.06 years and minimum 0.55 years. The above shows that the difference in time for assessment for marketing authorization between originator biologicals and biosimilars is insignificant.

Impact on prices of biologicals on the European market

The pharmaceutical industry plays a critical role in the global economy to produce innovative medicines through R & D [8]. The expenditure on R & D in Europe in 2017 reached 35.2 billion which nearly doubled since the year 2000 [26]. The European Federation of Pharmaceutical Industries and Associations (EFPIA) defends the high prices of biologicals attributing them to the high R & D costs, estimated in 2016 at 1,926 million (US$2,558 million dollars) [22]. Tuominen (2011) observed that originator companies still invest heavily in marketing and retain huge profits [20]. As per estimates by Gotham, the costs of manufacturing for the active ingredient (AI) of blockbuster drugs are “0.001%–6% of the current lowest prices in the US and 0.004%–14% of prices in the UK” [12]. Manufacturing companies invest only 15% of the profits in R & D whilst one- to two-thirds of R & D costs are covered through public funding, for example through Horizon 2020 and Innovative Medicines Initiative [4]. The EC confirmed that part of the research is publicly funded or funded through research facilities (universities and specialized laboratories of research) [26]. The Corporate European Observatory reported that monopolies are resulting in excessive prices of innovative biologicals which are disproportionate to the research and development costs, resulting in accessibility problems [4]. For example, the price for Humira® (the originator for adalimumab) in the US increased by 18% annually from 2012 to 2016 and also in later years as a result of monopoly [32].

The pharmaceutical industry further employs various strategies, termed as ‘*evergreening*’ to extend patent protection with the aim to retain monopoly [20]. These include patent ‘thickets’ or ‘clusters’, where the originator pharmaceutical company files in numerous patents for the same molecule, which may vary from a broad patent to more specific patents; secondary patents or follow-on patents, where the innovator company files for an application for improvement to the medicine, e.g. different formulation or a different salt, just before expiry of the patent so as to extend the product’s life cycle, presenting delays in competition, patent settlements or pay-for-delay, where an agreement is reached between the patent owner and alleged infringer to disrupt free competition [20]; withdrawal of the marketing authorization of the originator product and its replacement by a new formulation, such that generic companies cannot apply for an abridged marketing authorization [26]; downgrading the generic name, where the generic brands are given a bad name, influencing healthcare professionals against switching to generics or biosimilars [26]; mergers between originator and biosimilar companies, so as to achieve control over which product to place on the market preventing biosimilars from entering the market [26]; offering bonuses and other incentives to healthcare professionals to favour their products [4]; and collusion between competitors for price fixing, which involves hidden agreements between competitors for products within the same therapeutic class [4].

These strategies are indicative of a lack of transparency. Agreements or cartels between associations are prohibited by the Treaty on Functioning of the European Union (TFEU) as they may disrupt free competition within the internal market (Article 101), and may lead to abuses related to the dominant position on the market (Article 102) [4]. Regulation (EC) No 1/2003 empowers the EU Commission and National Competent Authorities to investigate any arrangements that do not observe the Treaty [33]. Due to different interpretations, in March 2017 the European Parliament called on the CJEU “to clarify, in accordance with Article 102 TFEU, what constitutes an abuse of a dominant position by charging high prices” which is not resolved yet [25]. The European Commission also called for more transparency in costs of R & D (including those obtained from public funding), costs for marketing, and monitoring and investigating patent settlements (pay-for-delay), and enforcement of EU competition legislation [25].

As per Article 168 (7) of the TFEU, Member States are free to set prices and policies for reimbursement of prescription medicines according to their economy through government [34]. National authorities may decide which treatments may be reimbursed under their social security system according to political and other priorities. For new medicines to be reimbursed, national authorities require marketing authorization holders to submit the price and usually there is negotiation. However, the set prices and negotiations are not linked to any prior public funding supporting the research phase.

Impact on the accessibility of the COVID-19 vaccine

The 2020 COVID-19 pandemic presented a global public health emergency which necessitated international cooperation to combat the SARS-CoV-2 virus. This required fast R & D of the COVID-19 vaccine candidates through vaccine technologies ranging from viral vector-based, protein-based, mRNA and lipid nanoparticle technologies [35].

The fast development of COVID-19 vaccines was possible as knowledge was transferred by scientists which allowed multiple companies and research companies to develop and bring to the market a number of COVID-19 vaccines within a year. Gaviria and Kilic (2021) claim that the COVID-19 vaccine technology is protected by a ‘web of intellectual property’, effecting equitable access and fair allocation [35]. The various technologies, namely, mRNA technology, lipid nanoparticle technology and delivery systems technology, are all covered by IP rights owned by large companies, which create legal barriers to the development of these vaccines by other manufacturing companies [35].

In October 2020, India and South Africa submitted an initial proposal for a temporary waiver of patents for COVID-19 vaccine to increase production to meet the global demand and thus provide access to the vaccine to all citizens in all countries. By April 2021, this was supported by 60 WTO members. In May 2021, the US Biden Administration supported these calls to drop intellectual protection for COVID-19 vaccines due to the global health crisis.

Pharmaceutical companies strongly objected to this proposal as they claimed that this would create a precedent and threaten future innovations [36]. Some European leaders and the UK Prime Minister opposed the patent waiver proposal, stating that transfer of knowledge to generic manufacturing companies is not sufficient as these companies lack the expertise in biological technology and workforce to build vaccine plants and would not guarantee the production of the vaccine [36].

Nevertheless, the EU Parliament in June 2021 voted in favour of the resolution that supports waiving the patent for COVID-19 vaccine, with some amendments. In June 2021, the WTO TRIPS Council agreed to move to the next stage of text-based negotiations of the India and South African proposal. Consensus needs to be achieved on the draft by the WTO General Council and a decision on the waiver is expected to be reached by December 2021 [37].

In parallel, in 2020, the EU set its COVID-19 strategy which included a joint procurement scheme to deliver vaccines across its 27 Member States and simplify the price negotiation processes with pharmaceutical companies once they reached authorization. This ensured timely, equitable, and affordable access to COVID-19 vaccines that meet quality, safety and efficacy EU standards for all European citizens [38].

Discussion

The biologicals market in the EU

Following marketing authorization, a medicinal product is launched on the market and follows the cycle through market growth, maturity and decline. Companies cannot produce generics for biologicals due to their nature. The EU introduced the biosimilar regulatory pathway for biologicals to achieve competition through biosimilars. The production of biosimilars involves reverse engineering and setting up a new cell line and manufacturing process. Companies are required to present phase III clinical trials data to EMA in order to provide assurance regarding clinical similarity to the originator [5]. The complexity of biosimilar development presents delays for them to reach the market, such that originator biological products do not face the 'patent cliff' as for chemically synthesised products [39].

The biosimilar regulations came into force in October 2005 through Directive 2004/27 [40]. Table 3 also shows the dates of coming into force of more specific biosimilar guidelines. One notes that only a few originator biologicals have biosimilars. Table 3 shows that only 17 active substances have authorized biosimilars, out of a total of 277 authorized biological active substances shown in Table 2. This means that only 6.14% of biological active substances have biosimilars. IQVIA (formerly Quintiles and IMS Health, Inc) claimed that only five biologicals dominated the loss of exclusivity over the period 2013–2018 [41]. This was confirmed in the data from Figure 2. The limited number of biosimilars could be attributed to the fact that it may be difficult to apply the biosimilar approach to biological medicinal products, 'which by their nature are more difficult to characterize, such as biological substances arising from extraction from biological sources and/or those for which little clinical and regulatory experience has been gained' [42]. One may of course argue that the delay in bringing biosimilars to the -market was a result of the fact that biosimilars could not be placed on the market before October 2005, for it was then that the legal basis for a biosimilar framework became possible through Directive 2004/27. However, Druedahl et al. (2020) report that lack of clarity in biosimilar approval requirements was identified as one of the regulatory barriers to biosimilar manufacturing companies, even despite the product specific guidelines developed by EMA [43]. Biosimilar manufacturing companies generally resort to seeking scientific advice from the regulators at various stages of the development process at an additional financial cost. The same authors report ambiguity with regards to the need for clinical trials for biosimilar development and generally, the decision is taken on a case-by-case basis. Biosimilar companies are also required to use novel study techniques as part of the development [43]. This implies that biosimilar companies face intellectual property challenges throughout the product development process, which could hinder the submission of applications for biosimilars [44]. Druedahl et al. (2020) reported that in 2017 EMA tried to address this issue through a pilot project on setting up a stepwise biosimilar development plan, which does not replace the need for biosimilar manufacturing companies to seek advice from EMA [43]. Scientific advice is sought prior to submission of the biosimilar application to EMA for authorization which is not reflected in the time for authorization by EMA including stop clocks. A further analysis of the date of submission of biosimilar applications in relation to patent expiry for the same biological as shown in Table 3 points to the fact that IP rights were also a major contributing factor until 2014. Since 2015 biosimilar companies started submitting application for biosimilars prior to patent expiry.

Intellectual property is affecting several aspects in the development process also for biosimilars. There could be other factors, for example, the fact that biologicals are quite sensitive to environmental and manufacturing conditions which are usually kept as trade secrets by the originator company. Moreover, novel studies required by the regulator may also be protected by intellectual property. Thus, although the EC attempted to bring competition by setting up the biosimilar regulatory framework, the EC's IP rights regulations continue to favour and protect the originator manufacturers.

It is projected that in the next 4–5 years a high number of products with valid protection status will lose exclusivity rights. These mainly represent smaller patient populations. Programmed cell death protein 1 (PD-1) inhibitors, which are forecasted to impact a large patient population, will also lose intellectual protection [41]. It is yet to be seen whether companies will find it feasible to develop biosimilars to these products.

Strategies to improve competition in the EU biological market

The Organisation for Economic Co-operation and Development (OECD) claimed that healthcare systems stand to benefit from competition of referenced (off-patent) biologicals and biosimilars [45]. IQVIA, reported that in 2020 biosimilar medicines reached €8.4 billion which represents 9% of the total biologicals market in the EU with a growth of 60% year-on-year [41]. The potential cost savings from biosimilars are projected to be US$54 billion over 10 years [46]. Nonetheless, pricing policies alone are not sufficient to increase biosimilar uptake [6]. Though price reductions of 50%–70% have been reported by IMS Health (2016) with some biosimilars, there is a poor correlation between the biosimilar market share and price reduction due to patients being switched to second-generation products, for example with erythropoietin (EPO) and granulocyte colony-stimulating factors (G-CSF), biosimilars [47] and insulins [41]. Focusing on biosimilar uptake alone is not a suitable solution [41]. It is therefore essential to bring biosimilars of the new biologicals earlier to the market to achieve sustainable competition, which would reduce market prices and thus improve access to biologicals. Thus, while the delay in authorization of biosimilars shown in Table 3 might be partly due to the lack of a biosimilar framework before October 2005, it remains imperative to remove as many barriers from the IP framework as possible to bring biosimilars to the market as early as possible, before second generation products are produced. The high prices of biologicals for smaller patient populations would also need to be addressed.

Recommendations for improvement of the EU IP framework

Knowledge sharing

The literature has shown that knowledge sharing which took place for the COVID-19 vaccines provided tangible advantages in terms of access to COVID-19 vaccines. This was essential to meet the global public health crisis brought about by the COVID-19 pandemic. It also presented advantages to the pharmaceutical industry which could not cope as the demand was too large for any one company to achieve on its own. Moreover, the novel therapeutics, especially the mRNA technology, reached the market quickly, without the need of high-level phase III clinical trials. It has also promoted the novel technology for future development of biologicals. Knowledge sharing should therefore be considered for biologicals where accessibility to essential treatment is considered to be a critical issue.

As seen in the literature, knowledge sharing may also be implemented by providing CLA to other manufacturers. Patency and exclusivity rights would still be retained by the originator company, which may benefit from remuneration from the CLA biological company for granting access to its CLA. This proposal would require further analysis from the legal and regulatory perspectives.

Patents and exclusivity protection incentives

Some authors report that there does not appear to be a link between the data and market exclusivity protections with innovation [22]. The

SPC framework in Europe is also considered to be complex and there is the risk that the SPC mechanism is being used as an '*evergreening*' strategy.

The regulations governing the EU IP framework thus need to be revised to reduce the complexity and bureaucracy of its framework which is leading to abuse of the incentive system.

The '*evergreening*' strategies are also responsible for extending patent validity. They need to be addressed through revisiting patent law, vis-à-vis what makes a product innovative and what makes it covered by a patent as a new product, so as to eliminate patent thickets and patent extension systems. The European Commission should also revise the legislation of the 'Sunset Clause' which allows market withdrawals. There should also be transparency on public disclosure of relationships between pharmaceutical industry and patient groups, institutions and healthcare professionals so as to ensure independent decision taking.

Moreover, as the IQVIA report [41] points out, biosimilars are only sustainable if their sales are sufficient to attain a return on investment. This is of course very important in the case of biologicals which target diseases relevant for small patient populations (orphan drugs). The designation of orphan drug status needs to be restricted to rare diseases only coupled by a revision of the prioritization of unmet clinical needs.

Excessive pricing for biologicals

The prices of biologicals depend on a number of factors, including demand-side factors which are not related to intellectual property rights. However, as evidenced in the literature [8], IP protection rights are a major contributing factor to monopoly, resulting in high prices of biologicals. The prices of biologicals are also disproportionate compared to the cost of development [4]. The question of public funding of research leading to private patents and private profits seems to escape scrutiny. One way of addressing excessive prices is through transparency.

Transparency of information on R & D costs and prices

The Commission has called for transparency in costs of R & D, including costs obtained from public funding. Sharing of data on prices of medicines by different Member States would be beneficial to governments towards fair pricing, i.e. the right balance between affordability and innovation. In May 2019, WHO launched the World Health Assembly Resolution 72.8 on Transparency [48]. In July 2021, WHO published a report on 'mechanisms for improving transparency of markets for medicines, vaccines and health products' which provides policy recommendations to Member States when negotiating prices for medicinal products [49]. These include implementing legislation on pricing transparency, using caution when entering in confidentiality agreements with manufacturers, implementing price regulation, monitoring and reporting, among others. In practice, the progress on the uptake of measures related to transparency seems to be quite slow and difficult and requires more commitment from European Member States. Literature has shown that joint procurement at EU level representing 27 Member States provides higher bargaining power to EU Member States in price negotiations with the pharmaceutical industry which could be utilized to achieve timely, equitable, and affordable access to biologicals [38].

Conclusion

The analysis confirmed a low percentage of biosimilar authorizations in Europe. It was also confirmed that there were significant delays in biosimilar authorizations, which were not related to the assessment of the marketing authorization process but were mainly attributed to the complexity in the development process and IP protection of the originator biological active substance, trade secrets for cell line and manufacturing processes, and the novel studies required in the biosimilar development process. The evidence in the literature points out that prescribers are moving to the new biologicals and thus price reductions are not necessarily being achieved with biosimilars. Focusing on the uptake of biosimilars is not considered sufficient to increase access to biologicals. The evidence from the literature confirms that the pharmaceutical industry benefits from the monopoly status of originator biologicals resulting from the various IP systems that protect innovation. This results in excessive prices of biologicals whereby the actual costs of the products are disproportionate to investment costs on R & D. Sharing of knowledge, for example, through CLA was identified as a possible solution, which could provide significant results, but requires further analysis. The definition of what constitutes an orphan drug appears to be too broad and should be re-defined whilst the prioritization of unmet clinical needs to be revised. The EU regulatory incentives require revision so as to provide protection to innovation without impacting accessibility. The '*evergreening*' strategies employed by pharmaceutical industry further extend the monopoly status. Incidents of potential abuse need to be investigated in a timely manner by ongoing monitoring and application of proportionate punitive action by the responsible competent authorities. In addition, a transparent pricing system capturing R & D costs and public funding of research should be introduced so as to achieve fair pricing with the aim to improve market access. The central EU joint procurement mechanism should be considered for biologicals as it provides negotiation power to the EU Member States.

This study confirms that the EU Pharmaceutical Strategy should prioritize the revision of the current EU IP system in order to achieve its aim of ensuring timely, equitable, and affordable access of biological medicines to all EU citizens. Unless changes to the EU IP system are implemented, the current status quo will not be addressed.

For patients

Once the patent of biological medicines expires, similar biological medicines, termed as biosimilars, can enter the market. Biosimilar medicines have similar effectiveness as the originator medicine but are 50%-70% cheaper. In view of the high prices of biological medicines, biosimilar medicines allow patients to access safe, effective and high-quality biological medicines at reduced prices of the branded originator medicines. The patent system is intended to allow originator companies to protect innovation as the industry would have invested heavily in R & D and manufacturing. Thus, the manufacturing company can recoup its investment costs and is also encouraged to continue to perform research for new medicines, to secure development of new medicines to treat diseases which so far are untreatable. The European Union also introduced other mechanisms to lengthen the patent protection period, such as supplementary protection certificate and data or marketing exclusivity. However, manufacturing companies started using strategies to further extend the patent period which exploit the legal framework such as '*evergreening*' which mainly involves multiple patent systems. The patent and other protection systems can stifle competition and create a monopoly thus contributing to the high prices of biological medicines. This is resulting in problems for patients to access biological medicines, for treatment of diabetes, cancer and other diseases. This review shows that the EU regulations for patent protection may not be supporting innovation to the expected levels and originator companies may be abusing of this system to extend monopoly status and keep their prices high. This review recommends improvements for mitigation of the negative effects from patents, such as sharing of knowledge between originator and other companies, a less complex regulatory framework for patenting in Europe and also transparent prices and costs related to the R & D and manufacturing costs and public funding. These aim to bring biosimilars to the market earlier thus improving accessibility of biological medicines to patients.

Funding sources

None.

Competing interests: None.
Provenance and peer review: Not commissioned; externally peer reviewed.

Authors

Josette Sciberras, MBA, MA Bioethics, BPharm (Hons)
Raymond Zammit, SThD
Patricia Vella Bonanno, PhD

References

1. Reilly MS, Schneider PJ. Policy recommendations for a sustainable biosimilars market: lessons from Europe. Generics and Biosimilars Initiative Journal (GaBI Journal). 2020;9(2):76-83. doi:10.5639/gabij.2020.0902.013
2. Derbyshire M, Shina S. Patent expiry dates for biologicals: 2018 update. Generics and Biosimilars Initiative Journal (GaBI Journal). 2019;8(1):24-31. doi:10.5639/gabij.2019.0801.003
3. Pharmaceutical Technology. The top-selling prescription drugs by revenue: Ranking the top ten [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.pharmaceutical-technology.com/features/top-selling-prescription-drugs/
4. Corporate Europe Observatory. Tansey R. High prices, poor access: what is Big Pharma fighting for in Brussels? May 2019 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://corporateeurope.org/en/2019/05/high-prices-poor-access-eu-medicines-market-and-big-pharma.
5. Espin J, Schlander M, Godman B, Anderson P, MestreFerrandiz J, Borget I, et al. Projecting pharmaceutical expenditure in EU5 to 2021: adjusting for the impact of discounts and rebates. Appl Health Econ Health Policy. 2018;16(6):803-17.
6. World Health Organization. Regional Office for Europe, European Observatory on Health Systems and Policies. Vogler S, Paris V, Panteli D. Ensuring access to medicines: how to redesign pricing, reimbursement and procurement? 2018 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.euro.who.int/en/about-us/partners/observatory/publications/policy-briefs-and-summaries/ensuring-access-to-medicines-how-to-redesign-pricing,-reimbursement-and-procurement
7. World Health Organization. WHO guide to identifying the economic consequences of disease and injury. [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https//www.who.int/choice/publications/d_economic_impact_guide.pdf
8. European Commission. A pharmaceutical strategy for Europe 2020 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://ec.europa.eu/health/human-use/strategy_en
9. Council of the European Union. Council conclusions on access to medicines and medical devices for a stronger and resilient EU. 16 June 2021 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://data.consilium.europa.eu/doc/document/ST-9750-2021-INIT/en/pdf
10. Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. Consolidated Document. 16.11.2012 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://ec.europa.eu/ health/sites/health/files/files/eudralex/vol1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf
11. European Medicines Agency. Medicines. Download medicine data [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.ema.europa.eu/en/medicines/download-medicine-data
12. Dzintars G. Cell line access to revolutionize the biosimilars market [version 1; referees: 2 approved]. F1000 Research. 2018;7:537.
13. Regulation (EEC) No 2309/93 of 22 July 1993 laying down community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, European Commission. Official Journal of the European Communities. 29/09/2003 L 245/19-21.
14. Directive (EU) 2016/943 of the European Parliament and of the Council of 8 June 2016 on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure. Official Journal of the European Union. 15.6.2016. L157/1-18.
15. Dechert LLP. Trade secrets in the life sciences sector. Lexology. 25 April 2018. [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.lexology.com/library/detail.aspx?g=09ecc65e-8daf-43d2-b131-48db583fb57d
16. Heled Y. The case for disclosure of biologics manufacturing information. J Law, Med Ethics. 2019;47(4):54-78.
17. Diependaele L, Cockbain J, Sterckx S. Similar or the same? Why biosimilars are not the solution. J Law, Med Ethics. 2018;46(3):776-90.
18. Publications Office of the European Union. Opinion on ethical questions arising from the Commission proposal for a Council Directive on legal protection for biotechnological inventions. Opinion of the Group of Advisors on the ethical implications of biotechnology to the European Commission. 30 September 1993 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://op.europa .eu/en/publication-detail/-/publication/a01f0708-252b-11e9-8d04-01aa75ed71a1/language-en/format-PDF/source-120515586
19. European Patent Office. Biotechnology patents at the EPO [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.epo.org/news-issues/issues/biotechnology-patents.html
20. Tuominen N. Patenting strategies of the EU pharmaceutical industry – crossroad between patent law and competition policy. European Legal Studies – Research Papers in Law 1. College of Europe. 2011:1-29.
21. Management Sciences for Health. Musungu S. Intellectual property and access to medicines. 2012 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.msh.org/sites/default/files/mds3-jan2014.pdf
22. The European Federation of Pharmaceutical Industries and Associations. The Pharmaceutical Industry in Figures – Key Data 2018. Brussels: EFPIA, 2018 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://efpia.eu/publications/downloads/efpia/2018-the-pharmaceutical-industry-in-figures/
23. Boulet P, Garrison C, 't Hoen E. European Union review of pharmaceutical incentives: suggestions for change. Medicines Law and Policy. June 2019.
24. GaBI Online – Generics and Biosimilars Initiative. Improving access to medicines: the Doha Declaration on the TRIPS Agreement [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2021 Sep 4]. Available from: www.gabionline.net/Generics/Research/Improving-access-to-medicines-the-Doha-Declaration-on-the-TRIPS-Agreement
25. European Parliament. Options for improving access to medicines – European Parliament resolution of 2 March 2017 on EU options for improving access to medicines (2016/2057(INI) No. P8_TA (2017)0061. 2017 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.europarl.europa.eu/doceo/document/TA-8-2017-0061_EN
26. European Commission. Report on competition enforcement in the pharmaceutical sector (2009-2017) [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://ec.europa.eu/competition/sectors/pharmaceuticals/report2019/index.html
27. Technopolis Group. De Jongh T, Radauer A, Bostyn S, Poort J. Effects of supplementary protection mechanisms for pharmaceutical products. 15 May 2018 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.technopolis-group.com/report/effects-of-supplementary-protection-mechanisms-for-pharmaceutical-products/
28. Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection

certificate for medicinal products. Official Journal of the European Union. 16.6.2009. L 152/1-10.
29. GaBI Online – Generics and Biosimilars Initiative. European SPC waivers come closer to becoming a reality [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2021 Sep 4]. Available from: www:gabionline.net/Guidelines/European-SPC-waivers-come-closer-to-becoming-a-reality
30. Hathaway C, Manthei J, Scherer C. Exclusivity strategies in the United States and European Union. Food and Drug Law Institute. 2009; (3):34-9.
31. Payette M, Grant-Kels JM. Brand name versus generic drugs: the ethical quandary in caring for our sophisticated patients while trying to reduce health-care costs: facts and controversies. Clin Dermatol. 2013;31(6):772-6.
32. Price II N, Arti K Rai. How logically impossible patents block biosimilars. Nat Biotechnol. 2019;37(8):862-3.
33. European Commission. Pharmaceuticals: EU refines intellectual property rules. 17 April 2019 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://ec.europa.eu/growth/content/pharmaceuticals-eu-refines-intellectual-property-rules_en
34. Consolidated version of the Treaty on the functioning of the European Union. Official Journal of the European Union. 26.10.2012. C 326-47.
35. Gaviria M, Burcu K. A network analysis of COVID-19 mRNA vaccine patents. Nat Biotechnol. 2021;39(5):546-9.
36. Moens B, Furlong A. European Parliament backs patent waiver for corona virus vaccines. Politico. 10 June 2021 [homepage on the Internet]. [cited 2021 Sep 4].Available from: https://www.politico.eu/article/european-parliament-backs-patent-waiver-for-coronavirus-vaccines/
37. Green A. WTO council offers hope for TRIPS vaccine proposal. Devex. 10 June 2021. [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.devex.com/news/wto-council-offers-hope-for-trips-vaccine-proposal-100125
38. European Commission. Coronavirus: Commission unveils EU vaccines strategy. 17 June 2020 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1103
39. Frank RG. Friction in the path to use of biosimilar drugs. N Engl J Med. 2018;378(9):791-3.
40. Directive 2004/27 of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal of the European Union. 30.04.2004. L 136/34-57
41. IQVIA (Intelligence-Quintiles-VIA I is taken from IMS Health or can be interpreted as Intelligence, Q comes from Quintiles or can be interpreted as Quotient and VIA is basically the path of transformation or a helping hand to achieve something) is an American multinational company serving the combined industries of health information technology and clinical research. IQVIA. White Paper – The Impact of Biosimilar Competition in Europe. December 2020.
42. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal product. Committee for Medicinal Products for Human Use (CHMP). 437/04 Rev 1. 23 October 2014.
43. Druedahl LC, Amarsdottir AB, Sporrong SK, De Bruin ML, Hoogland H, Minssen T, et al. A qualtitative study of biosimilar manufacturer and regulator perceptions on intellectual property and abbreviated approval pathways. Nat Biotechnol. 2020;38(11):1253-7.
44. Moorkens E, Jonker-Exler C, Huys I, Declerck P, Simoens S, Vulto AG. Overcoming barriers to the market access of biosimilars in the European Union: the case of biosimilar monoclonal antibodies. Front Pharmacol. 2016;7:193.
45. Simoens S, Le Pen C, Boone N, Breedveld F, Celano A, Llombart-Cussac A, et al. How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers. Generics and Biosimilars Initiative Journal (GaBI Journal). 2018;7(2):70-4. doi:10.5639/gabij.2018.0702.014
46. Gavrila R, Isaila M, Mircioiu C, Gherghiceanu F, Ghita I, Prasacu I, et al. Biostatic, legislative and ethical problems of comparative clinical studies. I. Generic and biosimilar drugs case. Farmacia. 2018:66(6):930-7.
47. Bocquet F, Loubière A, Fusier I, Cordonnier A-L, Paubel P. Competition between biosimilars and patented biologics: learning from European and Japanese experience. Pharmacoeconomics. 2016;34(11):1173-86.
48. World Health Organization. Improving the transparency of markets for medicines, vaccines and other health products. World Health Organization Seventy-second World Health Assembly 28 May 2019 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://apps.who.int/iris/handle/10665/329301
49. World Health Organization. WHO/Europe releases report on mechanisms for improving transparency of markets for medicines, vaccines and health products [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.euro.who.int/en/health-topics/Health-systems/pages/news/news/2021/7/whoeurope-releases-report-on-mechanisms-for-improving-transparency-of-markets-for-medicines,-vaccines-and-health-products
50. European Medicines Agency. Multidisciplinary biosimilar guidelines. 1 September 2021 [homepage on the Internet]. [cited 2021 Sep 4]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar

Author for correspondence: Josette Sciberras, MBA, MA Bioethics, BPharm (Hons), Room 204, Department of Moral Theology, Faculty of Theology, Humanities A Building, University of Malta, Msida MSD 2080, Malta

Disclosure of Conflict of Interest Statement is available upon request.

Name *

Mail *

Comments

Submit

Generics and Biosimilars Initiative (GaBI)
Tel: +32 474989572 / Fax: +32 14 583 048