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The cost savings of biosimilars can help increase patient access and lift the financial burden of health care systems

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ABSTRACT

Background: Biologics have provided improved clinical benefits to patients, but they come at a huge expense due to the high costs associated with their development and manufacturing. Biosimilars, which have been clinically studied and have demonstrated to be efficacious and safe, are more cost-effective versions of biologics, however, their uptake has been slow in the United States (US) compared to in the European Union (EU).
Objectives: In this analysis, we review the challenges to increased biosimilar use in the US and the successful strategies employed to increase biosimilar uptake in the EU.
Conclusions: Greater utilization of biosimilars in the US is an achievable goal but the federal government, pharmaceutical companies, and medical associations/institutions will need to work together to address patient and physician concerns and to remove incentives for using more expensive treatment options.

Introduction

Biologics have provided improved clinical benefits to patients, but they come at a huge expense due to the high costs associated with their development and manufacturing. These agents, which are genetically engineered proteins designed to target key elements and steps in a disease pathway, have proven safe and efficacious in the treatment of serious diseases, such as cancer and autoimmune diseases. However, access differs across countries and is related to economic parameters such as gross domestic product [1].

Biosimilars are more cost-effective versions of biologics but are not “generic” versions of their reference products. Generic drugs are exact copies of synthetically derived small molecule treatments. Biosimilars are much more complex, cannot be chemically synthesized on a commercial scale, and therefore are more expensive than generic drugs to develop. A generic may only cost $1 million to $4 million and take two years to develop vs $100 million to $250 million and seven to eight years for a biosimilar [2]. As of September 2021, there are 31 biosimilars approved in the United States (US) (Table 1) and 80 approved in the European Union (EU) (Table 2) [3–5].

Biosimilars could help alleviate some of the financial burden of care while still providing the same benefits of originator biologic treatments, [2,7] but their uptake in the US has been slow compared to most European countries as seen in Tables 1 and 2. This review will examine the challenges facing biosimilar uptake in the US, give examples of the steps needed to overcome these barriers and provide examples of successful implementation and use of biosimilars in European countries.

Biologic reference products and their approval processes

Biologics are large, complex proteins made from living organisms through highly complex manufacturing processes that involve the use of cell cultures. These processes can result in heterogeneous products with slight variations in production due to post-translational modifications, such as glycosylation and phosphorylation [8–10].

To earn US Food and Drug Administration (FDA) or European Medicines Agency (EMA) agreement to develop a drug, drug manufacturers must first complete a range of studies including animal and laboratory testing and repeat-dose toxicity studies that examine the pharmacokinetics (PK), pharmacodynamics (PD), and adverse events of the agent, and then submit an investigational new drug (IND) application to the FDA or a clinical trial application (CTA) to the EMA.

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Table 1
List of Biosimilars Approved in the United States [3].

Reference Product	Biosimilar/Manufacturer	Year Approved
Adalimumab	Hulio* (adalimumab-fkjp)/Mylan Pharmaceuticals	2020
	Abrilada* (adalimumab-afzb)/Pfizer	2019
	Hadlima* (adalimumab-bwwd)/Merck	2019
	Hyrimoz* (adalimumab-adaz)/Sandoz	2018
	Cyltezo* (adalimumab-adbm)/Boehringer Ingelheim	2017
	Amjevita* (adalimumab-atto)/Amgen	2016
Bevacizumab	Zirabev (bevacizumab-bvzr)/Pfizer	2019
	Mvasi (bevacizumab-awwb)/Amgen	2017
Epoetin	Retacrit (epoetin alfa-epbx)/Pfizer	2018
Etanercept	Eticovo* (etanercept-ykro)/Samsung BIOEPIS	2019
	Erelzi* (etanercept-szzs)/Sandoz	2016
Filgrastim	Nivestym (filgrastim-aafi)/Pfizer	2018
	Zarxio (filgrastim-sndz)/Sandoz	2015
Infliximab	Avsola (infliximab-axxq)/Amgen	2019
	Ixifi* (infliximab-qbtx)/Pfizer (Will not be marketed in US)	2017
	Renflexis (infliximab-abda)/Merck	2017
	Inflectra (infliximab-dyyb)/Celltrion/Pfizer	2016
Insulin glargine	Semglee (insulin glargine-yfgn)/Mylan Pharmaceuticals	2021
Pegfilgrastim	Nyvepria (pegfilgrastim-apgf)/Pfizer	2020
	Ziextenzo (pegfilgrastim-bmez)/Sandoz	2019
	Undenyca (pegfilgrastim-cbqv)/Coherus Biosciences	2018
	Fulphila (pegfilgrastim-jmdb)/Mylan	2018
Ranibizumab	Byooviz (ranibizumab-nuna)/Samsung Bioepis, Biogen	2021
Rituximab	Riabni (rituximab-arrx)/Amgen	2020
	Ruxience (rituximab-pvvr)/Pfizer	2019
	Truxima (rituximab-abbs)/CELLTRION for Teva Pharmaceuticals	2018
Trastuzumab	Kanjinti (trastuzumab-anns)/Amgen	2019
	Trazimera (trastuzumab-qyyp)/Pfizer	2019
	Ontruzant (trastuzumab-dttb)/Samsung BIOEPIS for Merck	2019
	Herzuma (trastuzumab-pkrb)/CELLTRION for Teva Pharmaceuticals	2018
	Ogivri (trastuzumab-dkst)/Mylan	2017

* These biosimilars are not available in the US as of November 19, 2020, due to patent protection of the reference product [6].

The FDA or EMA will then examine the biologic's pharmacologic effects and mechanism of action, as well as information on the product's absorption, distribution, metabolism, and excretion (ADME). After review of the data, the FDA or EMA will (if warranted) approve the proposed investigational drug for further testing in humans.

There is a three-phase clinical testing process utilized by the FDA and EMA. Phase I trials examine the product's metabolism, pharmacology, and safety at a single or escalating doses in humans. Phase II trials include proof-of-concept (efficacy), dose finding, and initial safety. Once the FDA or EMA deems the agent ready, it will enter into the third phase of clinical trials. In Phase III, randomized controlled trials (RCTs) are performed to ascertain clinical efficacy, additional outcomes, and adverse events in large groups of patients with various diseases where the biologic is expected to be effective [11,12]. Earning approval to market a drug is an expensive process, costing manufacturers approximately $1 billion to $1.8 billion [12].

In addition to clinical studies, characterization studies are performed to describe structural elements responsible for biological activity (e.g., active sites, receptor and ligand binding sites, features responsible for signal transduction). Any physico-chemical interactions between the active principle and its excipients are also investigated. Potential interactions between the product and primary packaging are studied to minimize any decrease in potency or biological activity of the finished product due to sorption that may occur during storage. Stability of the active substances should be investigated, including how the formulation and conditions employed in the manufacturing process and storage (e.g., relating to changes in temperature, pH, salt, pressure, shear) will impact the integrity of the molecule. Stability of the formulated product or the drug substance must also be studied under various process conditions [13].

Table 2
List of Biosimilars Approved in the EU [5].

Reference Product	Biosimilar/Manufacturer	Year Approved
Adalimumab	Yuflyma/Celltrion Healthcare Hungary Kft	2021
	Amsparity/Pfizer	2020
	Kromeya/Fresenius Kabi Deutschland	2019
	Idacio/Fresenius Kabi Deutschland	2019
	Hulio/Mylan	2018
	Hefiya/Sandoz	2018
	Halimatoz/Sandoz	2018
	Hyrimoz/Sandoz	2018
	Cyltezo*/Boehringer Ingelheim	2017
	Imraldi/Samsung Bioepis	2017
	Solymbic/Amgen	2017
	Amgevita/Amgen	2017
Bevacizumab	Abevmy/Mylan IRE Healthcare	2021
	Oyavas/STADA Arzneimittel	2021
	Alymsys/Mabxience Research SL	2021
	Onbevzi/Samsung Bioepis	2021
	Equidacent/PNR Pharma for Centus Biotherapeutics Europe	2020
	Aybintio/Biogen for Samsung Bioepis	2020
	Zirabev/Pfizer	2019
	Mvasi/Amgen	2018
Enoxaparin sodium	Inhixa/Techdow Pharma	2016
	Thorinane*/Techdow Pharma	2016
Epoetin alfa	Binocrit/Sandoz	2007
	Abseamed/Medice Arzneimittel Putter	2007
	Epoetin Alfa Hexal/Hexal AG	2007
Epoetin zeta	Retacrit/Pfizer	2007
	Silapo/STADA Arzneimittel	2007
Etanercept	Nepexto/Mylan	2020
	Erelzi/Sandoz	2017
	Benepali/Samsung Bioepis	2016

(*continued*)

Table 2 (*Continued*)

Reference Product	Biosimilar/Manufacturer	Year Approved
Filgrastim	Accofil/Accord Healthcare	2014
	Grastofil/Accord Healthcare	2013
	Nivestim/Pfizer	2010
	Zarzio/Sandoz	2009
	Filgrastim Hexal/Hexal AG	2009
	Filgrastim ratiopharm*/Ratiopharm	2008
	Biograstim*/AbZ-Pharma	2008
	Ratiograstim/Ratiopharm	2008
	Tevagrastim/TEVA	2008
Follitropin alfa	Bemfola/Gedeon Richter	2014
	Ovaleap/Theramex	2013
Infliximab	Zessly/Sandoz	2018
	Flixabi/Samsung Bioepis	2016
	Remsima/Celltrion	2013
	Inflectra/Pfizer	2013
Insulin aspart	Kirsty/Mylan Ireland	2021
	Insulin aspart Sanofi/Sanofi	2020
Insulin glargine	Semglee/Mylan	2018
	Lusduna/Merck	2017
	Abasaglar (previously Abasria)/Eli Lilly	2014
Insulin lispro	Insulin lispro Sanofi/Sanofi	2017
NovoRapid	Insulin aspart Sanofi/Sanofi-Aventis	2020
Pegfilgrastim	Nyvepria/Pfizer	2020
	Cegfila/Mundipharma	2019
	Grasustek/Juta Pharma	2019
	Ziextenzo/Sandoz	2018
	Fulphila/Mylan	2018
	Pelmeg/Mundipharma	2018
	Udenyca/ERA Consulting	2018
	Pelgraz/Accord Healthcare	2018
Ranibizumab	Byooviz/Samsung Bioepis	2021
Rituximab	Ruxience/Pfizer	2020
	Ritemvia/Biotec Services, Millmount Healthcare	2017
		2017
	Blitzima/Celltrion	2017
	Rituzena* (formerly Tuxella)/Celltrion	2017
	Rixathon/Sandoz	2017
	Riximyo/Sandoz and Lek Pharmaceuticals	2017
	Truxima/Celltrion	
Somatropin	Valtropin*/BioPartners	2006
	Omnitrope/Sandoz	2006
Teriparatide	Livogiva/Theramex Ireland Ltd	2020
	Qutavina*/EuroGenerics Holdings B.V.	2020
	Movymia/STADA	2017
	Terrosa/Gedeon Richter	2017
Trastuzumab	Zercepac/Accord Healthcare	2020
	Ogivri/Mylan	2018
	Trazimera/Wyeth and Pfizer	2018
	Kanjinti/Amgen	2018
	Herzuma/Biotech Services and Millmount Healthcare	2018
		2017
	Ontruzant/Samsung Bioepis	

* Product no longer authorized.

Biosimilars and their approval process

Biosimilars, although not identical, are highly similar to the reference biologic already licensed by the FDA or the EMA. There can be minor differences in some clinically inactive components between the biosimilar and reference product, but they must be highly similar in purity and potency, equivalent in efficacy and comparable in terms of safety [8,10,14-16].

Before a biosimilar can be approved, it must undergo rigorous testing [10,17-20]. Although the primary structure of the reference biologic is known, the manufacturing process is confidential between sponsor and regulatory agencies. The reverse engineering studies conducted to develop the biosimilar will yield extensive comparative data between the reference product and biosimilar, and will likely utilize newer, more advanced methods that were not available during the development of the reference product [17,21,22]. The approval processes of the FDA and EMA are similar for biosimilars. In the *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry* published by the FDA in 2015, it is mandated that structural analyses and functional assays be conducted. In vivo animal testing may also be performed including toxicology studies, PK and PD measures, and immunogenicity [18]. Comparative clinical trials are required to demonstrate PK and immunogenicity equivalence after a single dose between the reference product and the biosimilar, with clinical PK similarity needed for three endpoints: 1) maximum serum concentration; 2) area under the time-concentration curve from first to last time points measured; and 3) area under the time-concentration curve from first time point extrapolated to infinity [17]. At least one RCT is typically conducted in humans to determine equivalent efficacy, pharmacology, immunogenicity, and comparable safety data. These trials are conducted in at least one of the clinical indications for which the reference product is approved [18]. The designs of these studies are typically based on previous RCTs demonstrating the efficacy of the reference product. Biosimilars need to demonstrate equivalence to the reference product in these studies and not merely non-inferiority [17]. If a designation of interchangeability is desired, then a multiple switching PK/PD study must be conducted [19].

While the EMA requirements for biosimilar approval are similar to those for the FDA, there are two major differences – the EMA requires a post-marketing surveillance plan [10,20] and interchangeability or switching from a reference product to its biosimilar is ultimately decided by individual European countries and not by the EMA.

Biosimilar use: EU vs US

The EU is leading the way with regard to biosimilar approvals, utilization, and realization of cost savings [23,24]. Since the first biosimilar was approved in 2006, the EU has approved more treatments (80, see Table 2) over the last 15 years, more than anywhere else in the world [4,10]. In response to incentive programs instituted by individual member states, health authorities, and payers over the last few years, there has been a significant increase in biosimilar usage in the EU [10,20]. The United Kingdom's National Institute for Health and Care Excellence (NICE) and other decision-making bodies in countries in the EU use a health technology assessment (HTA) approach that considers cost efficacy and incremental cost efficacy ratios for health care reimbursement decisions [25]. This has led NICE to instruct British rheumatologists to begin treatment using the least expensive option. In Belgium and Germany there are quota systems that drive physicians to prescribe biosimilars in up to 40% of their patients [26]. In Norway, strong financial incentives to health systems to switch to biosimilars have resulted in 80% market shares for epoetin and filgrastim biosimilars [27,28] and even higher market shares for TNF-inhibitor biosimilars as described in Figs. 1A-1D**.** The systems in place in the EU countries are fostering increased use of biosimilars. This is in contrast to what is happening in the US where, out of the $126 billion spent on biologics in 2018, only approximately 2% was spent on biosimilars [29].

The cost of care

The growing use of expensive biologics has played a significant role in the continual rise of health care costs [16,25,30]. From 2013 through 2017, spending on biologics increased at almost twice the rate of small molecule drugs [30]. Although biologics account for approximately 2% of all US prescriptions, they represent almost 40% ($120 billion) of prescription drug spending [30]. To put the cost of biologics into perspective, the list price for a month's worth of biologic treatment for psoriatic arthritis can cost between $5000 and $12,000: Enbrel (etanercept) $5500 [31]; Cosentyx (secukinumab) $5500 [32]; Taltz (ixekizumab) $5900 [33]; Humira (adalimumab)

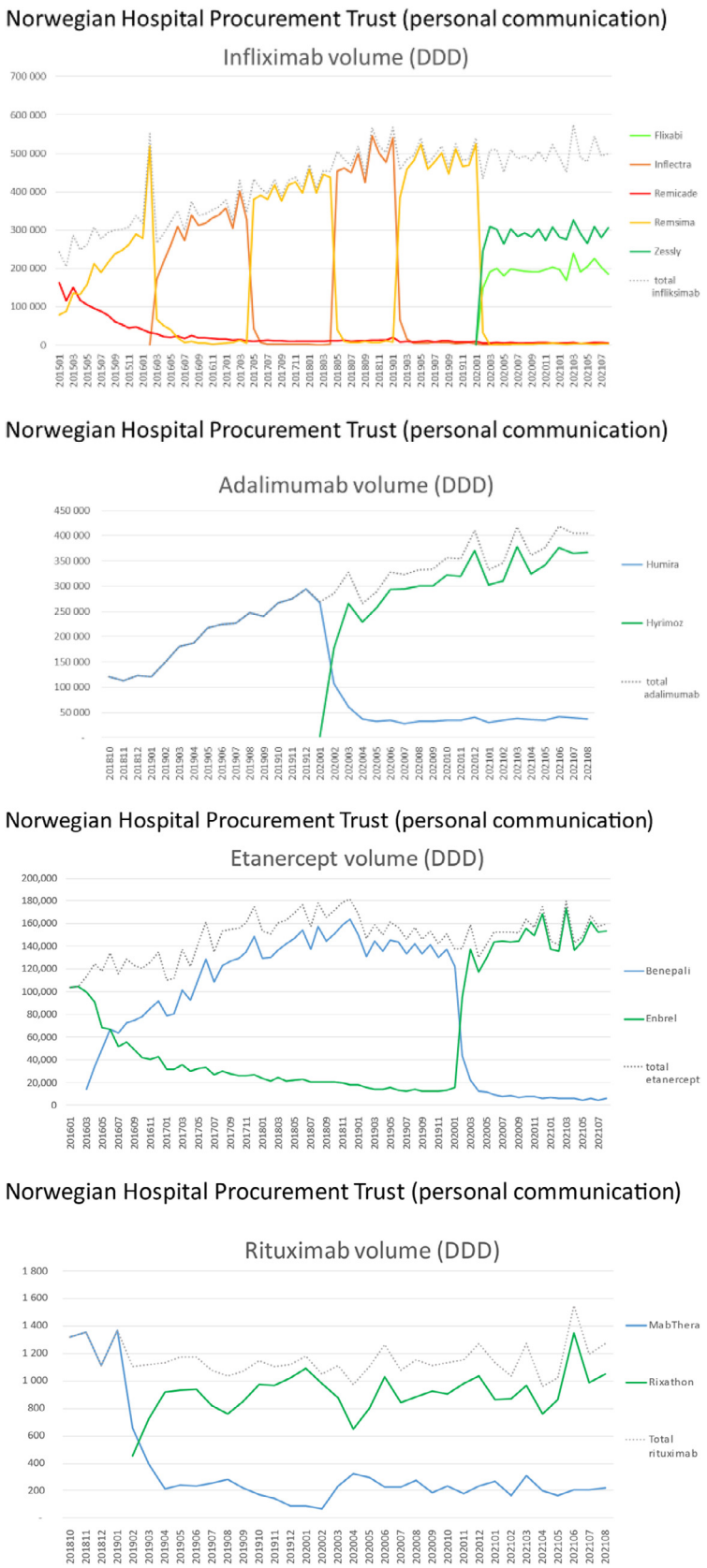

Fig. 1. The Uptake of Biosimilars and Originator Biologics in Norway Over the Last 5–6 Years. Volume data are defined daily doses (DDD) and are based on data from the Norwegian Hospital Procurement Trust [personal communications]. A. Infliximab and biosimilars (2015 to 2021) B. Adalimumab and biosimilar (2018 to 2021) C. Etanercept and biosimilar (2016 to 2019) D. Rituximab and biosimilar (2018 to 2021).

$6000 [34]; and Stelara (ustekinumab) $12,000 [35]. With at least 2 million Americans suffering from this one disease, [36] it is easy to see how these costs can quickly add up.

The financial ability of countries to deliver care, especially for cancer which in the US is estimated to cost $174 billion in 2020 and to exceed $245 billion by 2030, [37,38] was a concern for even high-income countries before the global economic slowdown brought on by the COVID-19 pandemic [25,39]. Use of less expensive biosimilars (which the Rand Corporation has estimated could save the US health system $54 billion over a decade) [7] can deliver the same efficacy and safety to patients while also providing significant cost savings and increased patient access to treatment.

Biosimilar cost savings: rheumatology

For the treatment of inflammatory arthritis, there are (as of September 2021) 15 biosimilars approved in the United States. Unfortunately, only seven rheumatologic biosimilars are marketed and available for patient use: infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), infliximab-abda (Renflexis), infliximab-qbtx (Ixifi), and three rituximab biosimilars (rituximab-abbs [Truxima], rituximab-pvvr [Ruxience], and rituximab-arrx [Riabni]). According to GoodRx.com (as of January 6, 2021), a single 100-mg vial of Remicade (infliximab) treatment can cost $1600 retail, vs $500 for Avsola, $900 for Inflectra (based on the purchase of a 4-vial set), and $740 for Renflexis (based on the purchase of a 5-vial set) (prices for Ixifi are not available). For the rituximab biosimilars, only Ruxience is available on GoodRx at a price of $7000 for two 50-ml vials (compared to almost $10,000 for Rituxan on Drugs.com [as of January 6, 2021]). This leads to savings with biosimilars ranging from 44% to 69% compared to the price of the reference drug. A Johns Hopkins study reported that patients prescribed an infliximab biosimilar ultimately paid 12% less out of pocket than with the reference biologic [40].

In the UK, France, and Germany, switching patients from infliximab to the biosimilar CT-P13 for rheumatoid arthritis was estimated to provide savings between 233 and 433 million Euros over a 5-year period (representing discounts of 20% and 30%, respectively). The savings from the 30% discount would be enough to support biosimilar treatment for over 7500 additional rheumatoid arthritis patients [26]. In Denmark, there is a tender system that creates competition between manufacturers of reference drugs and biosimilars. This system is very effective at controlling pricing – in 2019, AbbVie offered a price reduction of about 80% for Humira in the tender, which was still not good enough for it to gain exclusivity. This price reduction had ripple effects across Europe, especially in countries that have policies precluding them from paying more than other members of the EU [41].

Norway, since 2006, has had a national tender system for biologics, where each company offers a price for their product. Because these treatments have similar efficacy and safety on a group level, cost is now the major determinant for use. This applies to both new therapies and when switching therapies for medical reasons [42,43]. The budget for the cost of these drugs is now within the hospital system (biosimilars were covered by general reimbursement when they first launched), which enhances loyalty to the system [44]. Importantly, the system opens for exceptions in individual patients. For example, a patient may be prescribed a non-TNF inhibitor biologic if failing a TNF inhibitor without any anti-drug antibodies and normal drug levels or be prescribed an IL-6 inhibitor or a JAK inhibitor if intolerant of methotrexate [45].

This system has created increased competition that has impacted the uptake of biosimilars. When CT-P13 became available in 2014 the price was up to 39% lower than the originator, and one year later the price was up to 69% lower [26]. Figs. 1A-1D [personal communications] show the uptake of biosimilars and biologics for etanercept, infliximab, adalimumab, and rituximab over the last few years in Norway. Access has improved considerably: 100% for infliximab (2015 to 2021); >200% for adalimumab (2018 to 2021); 50% for etanercept (2016 to 2021); and stable for rituximab (2018 to 2021). The total cost has decreased by about $80 million in a population of about 5.5 million individuals, even if the use has been considerably increased.

There has also been a trend in Norway to start treatment earlier with biologic DMARDs and at a lower level of disease activity across all inflammatory joint diseases [46]. On average now, patients with rheumatoid arthritis will have low to moderate disease activity when a biologic DMARD is prescribed for the first time [46].

Obstacles to biosimilar uptake in the US

Biosimilars demonstrate comparable safety and equivalent efficacy to their reference products, and are less expensive. However, there are many challenges to greater acceptance in the US.

Reimbursement and rebates

The reimbursement of a drug is tied to the Average Sales Price (ASP), so the higher the ASP, the higher the reimbursement (Medicare Part B is set at 104.3% of ASP). In this system, a biosimilar with a lower ASP delivers a lower reimbursement than its reference product with a higher ASP [10].

Some Pharmacy Benefits Managers (PBMs) enter into agreements where they receive substantial rebates for using a reference product. Once this happens, they are vested in dispensing the reference product and have a reduced financial incentive to offer the less expensive biosimilar [10,47].

To prevent providers from facing this financial deterrent to prescribe lower-cost biosimilars, insurance programs have changed reimbursement policies to aggressively incentivize biosimilars through payment (detailed in section Health care systems).

Patent litigation

Many of the biosimilars approved by the US FDA face legal disputes brought by the reference product manufacturers who seek to delay the launch of the biosimilar, thus giving the reference product manufacturer a greater window of market exclusivity or share. One tactic is to file as many patents as possible for the biologic. For instance, as of August 2020, there are 136 Humira (AbbVie, Inc.) patents and 57 Enbrel (Amgen) patents [48–50].

For chemically manufactured drugs, the Drug Price Competition and Patent Term Restoration Act or the Hatch-Waxman Act, was enacted by Congress in 1984 to create a clear patent litigation framework for generic manufacturers. The act incentivizes generic manufacturers to challenge patents owned by brand manufacturers, and exempts generics from patent infringement liability for development work while patents for the brand are still in force [51]. Since Hatch-Waxman's enactment, the generic pharmaceutical industry has seen tremendous growth. For biologics, [52] a similar act has been enacted in 2010 to provide a patent dispute resolution process for biosimilars (detailed in section The US government).

Physician and patient concerns

In many countries, physicians and patients both express concerns with "switching", which is changing from the reference product or even changing back and forth between the reference product and the biosimilar agent, especially when the reason for the switch is cost oriented (known as "nonmedical switching"). In a 2019 survey sponsored by a reference product manufacturer, 84% of US physicians were opposed to switching a stable patient [10,53]. Some of the concerns that physicians have with switching are the possibility of increased immunogenicity, increased consultation time prior to

switching, and the need to extrapolate efficacy/safety data to different indications [54]. While we must acknowledge that these are real concerns, it is important to note that the risk of increased immunogenicity is at present purely hypothetical, as there have been no examples observed of an increase in immunogenicity after patients receive a biosimilar developed to the standards of the FDA or EMA. Education is needed to assure healthcare professionals and their patients that biosimilar treatment is actually a continuance with the same medication because it is a copy of the original biologic [55].

There are data available from phase 3 controlled clinical trials and extension studies to assuage physicians' concerns over switching. In the NOR-SWITCH Study that was financed by the Norwegian government, patients stable on the infliximab reference product were randomized to continued treatment with the reference product or switched from infliximab to CT-P13. Disease worsening (primary endpoint) was similar between the two groups (26% for the reference product; 30% for the biosimilar). Thus, switching was not inferior to continued treatment with the reference product and similarity was also demonstrated across all secondary endpoints, adverse events, and immunogenicity data [56]. In an extension study, no safety or efficacy concerns were raised for patients switching from infliximab reference product to CT-P13, compared to patients who maintained CT-P13 [57]. In a 2017 Danish study, 802 patients in the Danish DANBIO registry switched from infliximab to biosimilar CT-P13. The patients who switched had 28 Joint Disease Activity (DAS28) scores or Ankylosing Spondylitis Disease Activity Scores (ASDAS) similar to those seen while being treated with the reference product [58]. In a similarly designed study focusing on patients treated with etanercept in DANBIO, over 1600 patients made the switch and after 3 months disease activity was unchanged [59].

Patient reluctance to switching is usually tied to concerns over safety and efficacy [60,61] and a fear that a switch will occur without their knowledge or approval [55]. In a study of 222 Remicade-treated patients who agreed to transition to a biosimilar (CT-P13), 25% of patients discontinued use of the biosimilar due to an increase in subjective adverse events (based on the results of Disease Activity Score in 28 joints using the C-reactive protein level [DAS28-CRP] and Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]) that may be the result of the nocebo effect and/or incorrect causal attribution effects [62]. In a subsequent study, the same research group introduced a communication strategy about switching to reduce the risk of nocebo effect. With this design, drug retention improved [63–65].

Actions to increase biosimilar use in the US health care system

The US government

One path to increasing the number of biosimilars is to increase the number of approved biologics. In 2010, the US Congress enacted the Biologics Price Competition and Innovation Act (BPCIA) that created an abbreviated approval pathway for biologicals. This Act maintained 12 years of data protection in order to promote the development of new innovative biologics [8].

In 2018, a new Office of Therapeutic Biologics and Biosimilars (OTTB) was created to coordinate and improve activities under the Biosimilar User Fee Act (BSUFA) and promote the Biosimilar Outreach and Education Campaign (BOEC). The BSUFA authorized the FDA to assess and collect fees from biosimilar manufacturers in order to expedite the biosimilar review process. The purpose of the BOEC is to educate health care providers about biosimilars. Four key objectives are to: 1) improve the biosimilar development/approval process; 2) maximize scientific and regulatory clarity; 3) improve communication and education to health care providers regarding biosimilars; and 4) support market competition by reducing attempts to unfairly delay biosimilar approval and market entrance [10,66].

BPCIA has already provided a framework for the biosimilar applicant and the reference product sponsor to address any patent infringement concerns, similar to the Hatch-Waxman Act for generic drugs. This framework gives the biosimilar applicant substantial control over the timing and scope of a first patent litigation, which is then followed by a step-by-step exchange of contentions and negotiations [52]. However, interpretation of the BPCIA is still ongoing and courts have only begun to provide answers to speed the patent litigation process for biosimilars.

Healthy price competition can also increase the use of biosimilars. National tender systems such as those in Denmark and Norway [41–43] have increased competition, effectively controlled prices, and promoted the uptake of biosimilars. Policymakers in the US must also allow a system for robust competition between manufacturers of originators and biosimilars to drive prices of biologics down to the marginal cost of manufacturing, making them more affordable for patients.

Health care systems

To promote the prescription of lower-cost biosimilars, financial incentives to health care systems, like incentive programs instituted by individual member states in the EU [26–28], have been put into place to foster increased use of biosimilars in the US. BPCIA requires Medicare payment to include ASP of the biosimilar plus a fixed percentage based on the more expensive reference biologic [67]. This payment policy from Medicare and the similar 340B drug discount program have played a role in increasing biosimilar use. In this program, biosimilars are treated as innovator products and 340B hospitals are reimbursed at ASP of the biosimilar plus 6% of the reference biologic (vs ASP minus 22.5%), which allows 340B hospitals to potentially obtain higher payments for biosimilars than originators and incentivizes health care systems to use biosimilars [10, 68].

One health care system that has enjoyed the benefits of biosimilars is Kaiser Permanente. Kaiser's success is based on declining to accept rebates and being proactive in addressing the concerns that health care providers might have with regard to biosimilar safety and efficacy. By taking an evidence-based approach to formulary decision, and by including physicians in the process, health care providers are more comfortable and willing to switch to biosimilars. In one case, where gastrointestinal physicians were concerned about the safety and efficacy of infliximab biosimilars, Kaiser started a registry to allay these concerns. These efforts have paid off for Kaiser. When the bevacizumab biosimilar launched, it took only one month for Kaiser to achieve 97% uptake. As of November 2019, Kaiser has saved approximately $200 million since covering its first biosimilar [69]. The Veterans Administration system, which serves nine million veterans each year, has also made strides in taking advantage of biosimilars. In a study comparing biosimilar use in the Philadelphia VA Medical Center and the nearby University of Pennsylvania Medical Center, the VA hospital had prescribed the infliximab biosimilar 38% of the time vs only 1% for the academic institution [70,71].

Medical associations

Biosimilar use has also been promoted via the recommendations and guidelines of medical associations. In the 2013 update of the European League Against Rheumatism (EULAR) recommendations for use of DMARDs and bDMARDs, members were urged to consider costs when prescribing these therapies. Two years later, the American College of Rheumatology (ACR) also lent its support to cost considerations in their guidelines [26].

Few biosimilars approved for interchangeability

A biosimilar that is approved as interchangeable can be substituted by a pharmacist for the reference product without the knowledge of the initial prescriber. To achieve interchangeability status, the FDA requires an RCT that includes at least three switches between the biosimilar and reference product that demonstrates equivalent PK, PD, and immunogenicity [10]. All fifty states and Washington, DC, have already passed laws that permit or require pharmacists to dispense interchangeable biosimilars in certain situations, but that they do not do so without knowledge of the health care provider [72]. As of August 2021, Viatris (biosimilar to Semglee [insulin glargine-yfgn]) is the only interchangeable biosimilar approved in the United States; [73] Cyltezo (biosimilar to Humira) is expected to be approved later in the year based on the evidence shown in a phase 3 study [73,74].

Without interchangeability, prescribers must choose a specific biosimilar by name and pharmacists cannot substitute biosimilars automatically, which limit the potential for biosimilars to be adopted and compete on price with originators [67]. However, the complexity of the FDA's data requests for interchangeability puts a significant burden on manufacturers. [75] Relaxing the interchangeability standards, providing clarity on regulatory requirements and post-approval changes, and increasing funding opportunities for switching studies may encourage more biosimilar manufacturers seeking the interchangeable designation in the US.

Conclusions

"A billion here, a billion there, and pretty soon you're talking real money." This quote (reportedly made by a US Senator) summarizes the impact that the cost savings from biosimilars can have. A 20% discount on an analgesic that costs $10 does not amount to much. But if you take that same discount and apply it to a biologic that costs $40,000 — you now have savings that can help health care systems increase treatment access to more patients. Patients could directly benefit from the price competition and cost savings of biosimilars through lower insurance premiums and lower out-of-pocket costs, which enable more patients to choose to take the medication. [67] Providers, incentivized by drug discount programs such as 340B, may write more prescriptions of biosimilars for revenue [68]. Both increase the utilization of biological treatment for patients. Unfortunately, acceptance of biosimilars by physicians, patients, and payers has been suboptimal, particularly in the US. The EU has demonstrated strategies that work. In the US, we need to adapt those strategies to our health care system to alleviate some of its financial burden and to increase access of patients to medications that might otherwise be unaffordable to them.

Declarations of interest

None.

CRediT authorship contribution statement

Tore K. Kvien: Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Writing – review & editing. **Kashyap Patel:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Writing – review & editing. **Vibeke Strand:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Writing – review & editing.

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