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U.S. BIOSIMILAR MARKET ENTRY CHALLENGES AND FACILITATING FACTORS

FINAL REPORT

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LIST OF ABBREVIATIONS

351(a)	The section of the Public Health Service (PHS) Act under which original biologic products are licensed
351(k)	The section of the PHS Act under which biosimilar or interchangeable biologic products are licensed
AIC	Akaike information criterion
ANDA	Abbreviated New Drug Application
ARTG	Australian Register of Therapeutic Goods
ASP	Average sales price
BLA	Biologics License Application
BPCIA	Biologics Price Competition and Innovation Act
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Act
CAPM	Capital asset pricing model
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDMO	Contract development and manufacturing organization
CES	Comparative efficacy study
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, manufacturing, & controls
CMS	Centers for Medicare & Medicaid Services
CQA	Critical quality attribute
CRL	Complete response letter
CY	Calendar year
DAW	Dispense as written
ECBS	WHO Expert Committee on Biological Standardization
EMA	European Medicines Agency
ENPV	Expected net present value
ETASU	Elements to Assure Safe Use
EU	European Union
FDA	U.S. Food & Drug Administration
FIE	First interchangeable exclusivity
FSS	Federal supply schedule
GSK	GlaxoSmithKline LLC
HG-CSF	Human granulocyte colony stimulating factor
HHS	U.S. Department of Health and Human Services
HPFB	Health Canada Health Products and Food Branch
HSE	Health Service Executive
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational new drug
INN	International non-proprietary name

IP	Intellectual property
IQR	Interquartile range
IVF	In vitro fertilization
JAN	Japanese Approved Name
mAbs	Monoclonal antibodies
MG	Medication guide
NDA	New drug application
NDC	National Drug Code
NSP	National sales perspective
OTC	Over the counter
PAI	Pre-approval inspection
PBM	Pharmacy benefit manager
PD	Pharmacodynamic
PDUFA	Prescription Drug User Fee Act
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PNH	Paroxysmal nocturnal hemoglobinuria
PSG	Product specific guidance
PTAB	Patent Trial and Appeal Board; an internal USPTO entity that will hear and decide issues before disputants go to the expense and time of a federal courtroom trial
REMS	Risk Evaluation and Mitigation Strategy
RP	Reference product (RP) means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application
RPC	Reference product company; the company holding the patent(s) on a biologic
RTR	Refuse-to-receive
SME	Subject matter expert
SSE	Sum of squared errors
SSS	Single shared system
TBD	To be determined
TGA	Therapeutic Goods Administration (Australia)
TNF	Tumor necrosis factor
TRO	Temporary restraining order
USC	United States Code
USPTO	U.S. Patent and Trademark Office
VA	Veterans Affairs
VEGF	Vascular endothelial growth factor
WAC	Wholesale acquisition cost
WHO	World Health Organization

EXECUTIVE SUMMARY

There is ongoing interest in understanding ways to reduce drug prices and improve patient access to prescription drugs in the U.S. The estimated savings to the U.S. healthcare system from the use of biosimilars are significant. The Association of Accessible Medicines (AAM) estimated the savings to the U.S. healthcare system from use of biosimilars at $36.0 billion since 2015, which resulted in 495 million incremental days of patient therapy (i.e., patients who otherwise would not have gotten the therapy) over the same period [1]. Despite these findings, there is limited research on cost of biosimilar development; expected market uptake for biosimilar entrants; barriers that may affect market entry decisions; and potential incentives to encourage market entry. This study aims to fill that gap.

Biosimilars are in some ways like generic drugs; they have no clinically meaningful differences in safety, purity or potency compared to their reference biologics (or RPs). They were introduced to increase the competition and bring down prescription drug prices with the Biologics Price Competition and Innovation Act of 2009 that was enacted in 2010. However, biosimilars do differ from generics in that unlike generic developers, biosimilar developers still often need to conduct relatively large-scale clinical studies in humans, which greatly increases the cost and time to develop a new biosimilar. They also have been facing poorer market uptake in the United States compared to generics even though they are cheaper. First, they cannot always be automatically substituted in the same way as generic drugs, partly because of how they are reimbursed. Second, physicians and patients have been hesitant and concerned about whether the biosimilar is really the same as the RP. Third, there exists misaligned incentives in the pharmaceutical supply chain that favor RP manufacturers. For example, there are circumstances where higher-priced RPs are used because they yield more profit to supply chain intermediaries.

As of the end of 2024 there are 63 biosimilars representing 18 RPs in the United States. However, out of the 63 approved biosimilars 13 (about 21 percent have not yet launched in the market. Eight out of these 18 RP markets have only 1 or 2 biosimilars but four have six or more biosimilars. Additionally, there are a total of 80 biosimilars in development. Over half of these products are in the comparative efficacy study stage. However, the biosimilar pipeline varies across different markets due to factors like therapeutic area, disease prevalence, patent barriers, and pricing policies. High-demand areas such as oncology and autoimmune diseases attract more biosimilar development due to large patient populations and significant spending. In contrast, biologics for rare diseases see fewer biosimilars because of smaller patient populations and limited returns on investment. Extensive patent protections can complicate biosimilar development, increasing costs. Unfavorable reimbursement structures, like the “buy-and-bill” model under Medicare Part B, slow biosimilar uptake, while payer incentives and effective formulary placement, such as the CMS Oncology Care Model, support robust pipelines. Market saturation also affects biosimilar entry, with crowded markets being less attractive for additional development.

Using public and proprietary data sources combined with insights from subject matter experts (SMEs), we analyzed the biosimilar development process and factors affecting cost,

success probability, and time at each development stage. We then created a valuation model to estimate the expected net present value (ENPV) of launching a biosimilar in the United States, considering failure and capital costs, market size variations, competition, and product complexity. Using the model developed, we then examined the impact of select barriers and incentives on ENPV.

Key findings of our study include the following:

- Market size and entry order significantly influence the revenues of an average biosimilar throughout its market life. In large markets (> $1.0 billion in annual sales), the lifetime ENPV ranges from $9.5 billion for the first entrant to $1.3 billion for the fourth and fifth entrants. In medium sized markets, the first biosimilar's lifetime ENPV is $1.5 billion, but it drops to –$38.7 million for the fourth and fifth entrants. For markets smaller than $500 million, the lifetime ENPV is consistently negative for all entrants, ranging from –$33.5 million for the first entrant to –$266.5 million for the fourth and fifth entrants. This finding aligns with the observation from several SMEs that $500 million is the minimum RP market size a biosimilar company might consider entering.
- Designating all approved biosimilars as interchangeable has a sizable impact on ENPV. BPCIA established an interchangeable designation for biosimilars, which could be earned by submitting additional clinical switching studies. We used generic drug uptake data to estimate the faster uptake that would occur with universal interchangeable designation for biosimilars. Although development costs remained unchanged, the improved uptake rate increased the lifetime ENPV for a biosimilar company by $2 billion, or 20.6 percent in large markets.
- Establishing a global comparator can significantly streamline the biosimilar development process by removing the necessity for a bridging study to confirm the identity between the FDA-approved RP and a foreign-sourced RP. This approach results in an estimated cost savings of $5.1 million (4.5 percent) and a modest increase in the lifetime ENPV by $13.5 million. By using a global comparator, biosimilar developers can bypass additional testing requirements, thereby accelerating the development timeline and reducing associated costs.
- Eliminating the requirement for comparative efficacy studies (CESs) can lead to cost savings and an increase in lifetime ENPV in large markets. Specifically, the cost savings amount to $24 million (17.8 percent), while the lifetime ENPV increases by $84 million. CESs are the most expensive component of preparing a biosimilar for market entry. However, in their absence, more robust in vitro and PK/PD similarity studies will be necessary to address any remaining uncertainties about the biosimilar.

The landscape of biosimilar markets is continuously evolving so future research could focus on several key areas. First, evaluating biosimilar formulary coverage in hospitals and pharmacies could provide insights into accessibility and adoption rates. Additionally, comparing patient and physician hesitancy for biosimilars that treat chronic versus acute conditions could help identify barriers to acceptance. It is also crucial to compare adverse event profiles for

biosimilars approved with versus without comparative efficacy studies (CESs). Assessing changes in adoption and revenues for newer biosimilars will offer valuable data on market dynamics. Finally, investigating biosimilars in mid-sized markets as they increase in frequency may highlight emerging opportunities for potential market entrants.

1 INTRODUCTION

The U.S. Department of Health and Human Services (HHS) maintains an active interest in understanding ways to reduce drug prices and improve patient access to prescription drugs, specifically biological products, commonly known as "biologics."[1] Biologics are usually derived from living sources (such as animal cells, bacteria or yeast). This makes them complex in structure and generally more complicated to characterize than chemically synthesized drugs, which usually have a smaller structure and can be more easily characterized. It also can make them more expensive to manufacture than small molecule drugs. Like most drugs, biopharmaceutical companies conduct nonclinical and clinical research to develop a new biologic which is an expensive undertaking [2]. In return for this investment, new biologics generally receive patent and exclusivity protections against certain forms of competition. Once any relevant exclusivity period(s) expire, the Biologics Price Competition and Innovation Act (BPCIA) of 2009 (enacted in 2010) allows other companies to market "biosimilar" versions of these products [3].[2]

In this study, we use the terms "biosimilar" and "interchangeable" as shorthand for biosimilar biologic; to describe a biologic product whose developer has the intent to submit or has submitted an "abbreviated" biologics license application (BLA) to U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) using the 351(k) approval pathway established by the BPCIA. Biosimilar companies compete in the market of a specific original approved biologic by developing and manufacturing a biosimilar that is both "highly similar to" and has "no clinically meaningful differences in safety, purity or potency (safety and effectiveness)" with the reference product (RP), in accordance with FDA standards [4]. We use the term "original biologic" to indicate a biologic product whose manufacturer submitted a BLA using the 351(a) pathway intended for new, innovative biologic products that

[1] In this document, "biological products" is intended to refer to human drugs that are licensed through the Center for Drug Evaluation and Research (CDER), such as therapeutic proteins, including monoclonal antibodies, insulins, etc., not to those regulated by the Center for Biologics Evaluation and Research (CBER), such as blood products, vaccines, and cell and gene therapies. [158]

[2] BPCIA is often viewed as analogous to the Hatch-Waxman amendments of 1984, which created the scientific and legal framework that facilitated the entry of generic drugs into brand drug markets. Both legislations established a less burdensome path to FDA approval compared to the paths faced by new brand drugs and original biologics; both established a pro forma patent infringement action that facilitates early resolution of patent disputes; both provide incentives to generic and biosimilar companies to challenge the patents held by brand and RP companies; and both provide branded RPs with several years of marketing free of generic or biosimilar competition. Hatch-Waxman provides that FDA will not approve a generic drug until at least 5 years have elapsed after a brand drug is approved for the first time; BPCIA guarantees that no biosimilar will be approved until 12 years after any reference product is approved, with certain exceptions. These periods of "regulatory exclusivity" are independent of the protections afforded by patents.

are not referencing a previously approved biologic.[3] And, we use the term "reference product (RP)" to mean an original biologic that a biosimilar company has selected as the comparator for its biosimilar product.[4]

The BPCIA established a new approval pathway, under section 351(k) of the Public Health Service Act, for biosimilar and interchangeable biological products (herein referred to as "biosimilars" and "interchangeables," respectively). A biological product may be demonstrated to be "biosimilar" if data show that (1) the product is "highly similar" to the RP, notwithstanding minor differences in clinically inactive components, and (2) there are no clinically meaningful differences between the biological product and the RP in terms of safety, purity and potency [3]. To meet the standard for interchangeability, a sponsor must also demonstrate that the biosimilar can be expected to produce the same clinical result as the RP in any given patient and, if the RP is typically administered more than once, that the risk of alternating or switching between use of the biosimilar and the RP is not greater than the risk of maintaining use of the RP [3, 5].[5] State laws cannot bar pharmacists from dispensing the interchangeable when filling prescriptions for the RP without consulting the prescriber.[6] Demonstrating biosimilarity generally involves a limited set of clinical studies compared to the full complement of clinical and nonclinical studies required for RPs. For example, an RP may be approved for multiple indications, each based on results from clinical studies demonstrating safety and effectiveness in the indicated patient populations, whereas a biosimilar can be approved for those same indications based on a set of data that may include only one clinical study in patients. Therefore, biosimilars and interchangeables ought to be considerably quicker and less expensive to develop.

An RP and its biosimilar or interchangeable competitors are expected to compete mainly on price, though certain factors under the control of third parties, such as availability, formulary access, etc. also may have a significant impact on pricing decisions. Nevertheless, research has shown that increasing the number of competitors in a given market both reduces the prices of biosimilars and places a downward pressure on the price of the RP.[7] This, in turn, reduces

[3] FDA says, "Section 351 of the *Public Health Service (PHS) Act* defines a biological product as a 'virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, … applicable to the prevention, treatment, or cure of a disease or condition of human beings.' FDA regulations and policies have established that biological products include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products" [159].

[4] FDA refers to a brand drug that one or more generics may rely on for approval as a Reference Listed Drug. See 21 CFR 314.3(b) (defining reference listed drug). Such drugs may also be referred informally as reference products. To eliminate any potential confusion, our scope is limited to original biologic and biosimilar markets, and in this document, "reference product (RP)" means an original biologic targeted by a biosimilar.

[5] FDA has begun to issue some product specific guidances, which may change these requirements. For example, FDA issued a guidance for insulin explaining that comparative clinical immunogenicity studies may not be needed to support licensure of proposed biosimilar and interchangeable recombinant human insulins, recombinant human insulin mix products, and recombinant insulin analog products that are intended for the treatment of patients with Type 1 or Type 2 diabetes mellitus (collectively described as "insulin products") [161].

[6] This designation is unique to the United States.

[7] Because interchangeables have not been on the market for a sufficiently long period, comparable evidence for interchangeables is lacking.

overall spending on these products. For example, Mulcahy et al. [6] estimated the total savings in seven RP markets due to biosimilar competition at $11.2 billion from 2015 to 2020. Savings were expected to increase substantially between 2020 and 2025 on the assumption that the rate of biosimilar approvals and launches would increase dramatically [6, 7, 8].

By the end of 2024, FDA had approved a total of 63 biosimilars, representing 18 RPs (or 17 RPs if Prolia and Xgeva are counted as a single RP). Of these 63 biosimilars, 42—representing 12 RPs—had been launched into their markets by the end of CY 2024. In 2023 alone, the savings attributed to biosimilars were $12.4 billion, and the total savings since 2015 reached nearly $36 billion [1].[8] In 2024, FDA approved 18 biosimilars; three of them launched in 2024, and seven more announced plans to launch early in 2025.

Despite these gains in savings, and the increased patient accessibility associated with more competitive prices, uptake of biosimilars (and concomitant savings) in some markets has fallen short of some earlier predictions [9]. Nevertheless, the success of biosimilars in providing significant savings to date highlights their potential to promote competition and lower biological product prices in the future. Further, any efforts to increase biosimilar and interchangeable competition will benefit from an improved understanding of the costs of developing these products, the barriers that may increase these costs, and policies that may encourage entry into the market.

To date, research on the cost of biosimilar and interchangeable development and approval has been limited. Further research is needed to evaluate whether additional policies or refinements are needed to incentivize biosimilar and interchangeable development. This study seeks to describe the key steps required to bring both a biosimilar and an interchangeable to market; describe major barriers that may affect decisions to enter a market; and factors that influence the cost and time spent at each step in the process. To accomplish these objectives, we developed an analytical framework and valuation model to account for all opportunity costs, including cost of capital, facility setup costs (and costs associated with setting up necessary manufacturing relationships), product development costs, testing costs, regulatory submission costs, costs of dealing with intellectual property (IP) rights, potential revenues, and the cost of maintaining approval once in the market (such as required post market submissions and reports to the FDA). The model also evaluates barriers and market factors to calculate an estimated expected net present value (ENPV) for a biosimilar and interchangeable. The results of this study are intended to aid FDA and HHS in designing policies aimed at increasing competition in biologic markets.

The remainder of this report is organized as follows. Section 1 describes the background and context for several important issues surrounding approval and uptake of biosimilars, including how biosimilar interchangeability has been approached in the United States and other countries; the need for clinical studies of proposed biosimilars; biosimilar uptake rates; list of all

[8] There are several elements to the computation of savings attributable to biosimilars. The main factor involves the difference between the cost of all biosimilars sold in the market plus the RP and what the cost would have been had that volume of products been sold at the price of the original biologic just before biosimilar competitors first entered the market.

FDA-approved biosimilars as of January 2025; and a description of the biosimilar pipeline. Section 3 presents the objectives of our effort to create a functional model of the cost and expected revenue of bringing a biosimilar to the U.S. market. Section 4 describes our analytic framework for biosimilar development costs; the model's parameters and assumptions—including 12 major cost variables, from cost of capital to preapproval inspection, our analysis of lifetime biosimilar revenues, the revenue model's parameters and assumptions, and the model's calculation of ENPV. Section 5 presents the results of running the model under various scenarios. Section 6 comprises an analysis of three major barriers to market entry that have confronted a proposed biosimilar, as well as three potential incentives. Barriers have included the impacts of BPCIA's interchangeability designation, patent thickets and associated patent issues, and the need to provide clinical efficacy study (CES) results when/if requested by FDA. The barriers analysis focuses on estimating the impact of these on biosimilar development costs. Incentives analyzed for their value to the biosimilar entrant include elimination of the interchangeable designation, acceptance of a global comparator biologic by FDA, and elimination of the requirement for data from a CES. The incentive analysis considers the impact of these incentives on the lifetime revenues for a biosimilar entrant in addition to their impact on development costs. For the purposes of this analysis, the only distinction to be made between an incentive and the removal or mitigation of a barrier is the difference—if there is one—in their potential effect on projected costs and revenue. Section 7 concludes with a discussion of main findings, study limitations, and areas for further research.

2 BACKGROUND

2.1 Biosimilar Markets in the United States and Rest of the World

The complex structures of biologics and their sensitivity to manufacturing conditions sets them apart from chemically synthesized drugs and have prompted a high level of international coordination of regulatory guidelines among governmental regulatory agencies. Europe led global regulators by establishing the first biosimilar regulatory pathway several years ahead of the United States. The first regulatory authority was passed by the European Medicines Agency (EMA) which established a regulatory pathway for biosimilar approval in 2005 and first approved a biosimilar in 2006 [10]. The World Health Organization (WHO) Expert Committee on Biological Standardization (ECBS) and the Japanese Ministry of Health, Labor and Welfare issued their initial guidances on biosimilars in 2009, followed by Health Canada in 2010 and FDA in 2012. India first approved a "biological similar" in 2000 (a vaccine for hepatitis B, Biovac-B) and a non-vaccine biological similar in 2001 (Wepox, or epoetin alfa, an erythropoiesis-stimulating agent used to treat anemia, especially in cancer patients). However, India's Central Drugs Standard Control Organization and the Department of Biotechnology did not develop their "Guidelines on Similar Biologics; Regulatory Requirements for Marketing Authorization in India" until 2012 (revised in 2016). FDA's first biosimilar approval was Zarxio (filgrastim-sndz) manufactured by Sandoz, which is a biosimilar to Neupogen (filgrastim), on March 6, 2015.

Klein et al. [11] examined biosimilars approved in five major markets—United States, EU and UK, Japan, Canada, and Australia—as well as biosimilars approved in 15 countries in

different regions of the world.[9] As of November 2023, there were a total of 272 biosimilars approved for marketing in the five major markets studied by Klein et al. [11] (see Table 1). The EU and UK market has the highest number of biosimilars approved (106) and currently marketed (89), followed by Australia and United States with 63 biosimilars approved (61). Tables listing approved biosimilars in all these five markets appear in Appendix A. Table 57 shows EMA approved biosimilars in Europe, Table 58 lists biosimilars approved by Health Canada, Table 59 lists Pharmaceuticals and Medical Devices Agency (PMDA)-approved biosimilars in Japan, and Table 60 lists biosimilars approved in Australia. There are numerous biosimilars approved outside these five major markets, including in India and China, but most of these products are licensed only in their country of manufacture.

Table 1. Number of Biosimilars in Five Major Markets (EU and UK, United States, Japan, Australia, and Canada) as of November 2023

Market	Regulatory Authority	Number of Approved Biosimilars	Number of Biosimilars Currently Marketed	Number of Reference Products (RPs) [a]
EU and UK	European Medicines Agency (EMA)	106	89	25
Australia	Therapeutic Goods Administration (TGA)	63	n/a	16
United States	Food and Drug Administration (FDA)	63	41	17
Canada	Health Canada Health Products and Food Branch (HPFB)	56	48	17
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	35	n/a	17
Total		**274**	**n/a**	**n/a**

n/a = not available/not applicable

[a] The number of marketed RPs might be lower than reported.

The United States (FDA), European Union (EMA), and Japan (PMDA) were all founding regulatory members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Since 2004, ICH has issued several guidelines on biologic development, evaluation, quality control, and manufacturing. Over the past 10 years, efforts to harmonize standards for evaluating biosimilars among regulatory bodies have diminished or eliminated most distinctions in regulatory approaches.

Operationally, the differences in regulatory bodies' biosimilar evaluation seem minimal. A recent study by Ingram et al. [12], sponsored by Pfizer, analyzed evaluations by four regulatory agencies—FDA, EMA, Health Canada Health Products and Food Branch (HPFB), and Japan's PMDA—of a portfolio of eight biosimilars submitted to them for approval. Three of the biosimilars were evaluated by all four agencies. The authors commented that "the biosimilar guidance and regulatory requirements for the four [regulatory agencies] covered by this analysis were largely aligned, with only minimal divergence to meet country-specific content requirements." Ingram et al. [12] also noted that, since EMA's initial guidance on biosimilars appeared in 2004, "a dedicated regulatory framework for such products has spread rapidly across the world, with biosimilar-specific regulatory paradigms currently established in over 20 countries."

[9] The 15 countries were: China, India, Indonesia, Malaysia, South Korea, South Africa, Tanzania, Argentina, Brazil, Chile, Columbia, Iran, Russia, Saudi Arabia, and Turkey.

2.2 Interchangeability

Despite their parallel regulatory frameworks, EMA and FDA policies differ in at least one important regard, viz., the operational definition of "interchangeable." BPCIA created a separate standard for those products meeting additional statutory standards intended to support that the product may be substituted for the RP without the intervention of the health care provider who prescribed the RP. FDA's initial guidance on interchangeability recommended that to gain interchangeable status, a sponsor conduct a clinical switching study to assure that switching from the RP to the biosimilar is comparable in safety and efficacy to the continued use of the RP [2]. Later updates to FDA's guidelines also enabled sponsors to use non-US licensed versions of the RP (i.e., a non-US comparator product)[10] in their switching studies, if they could provide a bridging study that justified using the non-US licensed comparator [13]. Recently, FDA issued a draft guidance to update the interchangeability guidance to explain that a clinical switching study is generally no longer needed to demonstrate interchangeability [14]. This change was based on a number of factors, including the experience FDA gained reviewing biosimilar and interchangeable biosimilar products.[11] The first product to receive approval as a biological product as interchangeable with an RP may qualify for first interchangeable exclusivity.[12] FDA may not approve a subsequent biological product as interchangeable with the same RP prior to the expiration of first interchangeable exclusivity.

In addition to the term "interchangeable" having an implicit marketing advantage over "biosimilar," states may not bar pharmacists from substituting an interchangeable when filling a prescription for the RP in the retail setting, without approval by the prescriber.[13] While automatic substitution may not always be applicable to those products dispensed in non-retail settings (e.g., hospital, outpatient clinic), interchangeability designation may increase provider/patient trust thereby leading to increased utilization. Thus, one would expect that these factors would increase sales for the interchangeable, even more so for the first interchangeable during its period of market period exclusivity without competition from another interchangeable.

At the end of December 2024, seventeen biosimilars were designated as interchangeables by FDA, six referencing Humira (adalimumab); two referencing Lucentis (ranibizumab) Lantus (insulin glargine), and Eylea (aflibercept) each; one referencing Enbrel (etanercept), Soliris (eculizumab), Prolia (denosumab), Xgeva (denosumab) and Stelara (ustekinumab) each. Owing to settlements, licensing agreements, or very recent approvals, only Cimerli (ranibizumab-eqrn) and Semglee (insulin glargine-yfgn) have launched into their markets long enough to begin to generate appreciable sales data (over $100 million in annual

[10] Non-licensed in this context means that the RP is licensed in a country other than the United States.
[11] As of June 2024, among 13 interchangeable products FDA approved, nine were approved without the need for a clinical switching study.
[12] Timing for expiration of this exclusivity depends on factors outlined in statute.
[13] In the United States, 45 states have passed legislation that requires or permits pharmacists to fill prescriptions for a biologic with an interchangeable (if one is available) without consulting the prescriber. In EU jurisdictions where this has been permitted, pharmacists generally consult the prescriber before making a substitution. Physicians can also note "dispense as written" on the prescription form to prevent unwanted substitution.

sales) to assess the relative value of the interchangeable designation and the accompanying term of exclusivity enjoyed by the first interchangeable in the market.

Four markets now have two or more interchangeables each, a situation that has generated legal questions about when exclusivity expires for the first interchangeable and for which products the first "interchangeable" blocks approval. Section 351(k)(6)(A), (B), and (C) of the PHS Act provides that FDA cannot approve a subsequent biological product as interchangeable with a RP until the earliest of any of the following dates [15]:

> (A) One year after the first commercial marketing of the first approved interchangeable;
>
> (B) 18 months after either (i) a final court decision on all patents in suit in an action instituted under subsection *(l)*(6) against the applicant that submitted the application for the first approved interchangeable; or (ii) the dismissal of such an action against the applicant; or
>
> (C) (i) 42 months after approval of the first interchangeable if the applicant has been sued under subsection *(l)*(6) and litigation is still ongoing within such 42-month period; or (ii) 18 months after approval of the first interchangeable if the applicant has not been sued under subsection (*l*)(6).

Unfortunately, as the recent FDA memorandum on this issue notes [15], the drafters of section 351(k)(6) did not foresee that a biosimilar applicant might first seek approval as a biosimilar and later submit a supplemental BLA for interchangeable status, with 351(l)(6) litigation concluding in the interim.[14] This was precisely the case with Boehringer Ingelheim's Cyltezo (adalimumab-adbm) and Pfizer's Abrilada (adalimumab-afzb), two products approved as biosimilars of Humira (adalimumab) in 2017 and 2019, respectively, and as interchangeables in 2021 and 2023, respectively, and 351(*l*)(6) litigation concluding in the interim between the approval of Cyltezo as a biosimilar and the submission of an interchangeability supplement. Both companies submitted memoranda to each other and FDA presenting different interpretations of how first interchangeable exclusivity (FIE) should be calculated. Put simply, Pfizer argued that because there was no 351(l)(6) litigation over Boehringer's supplemental application for interchangeability, there was no 351(l)(6) litigation for the purposes of section 351(k)(6). Therefore, Cyltezo's FIE expired 18 months after it was approved as an interchangeable, as per 351(k)(6)(C)(ii). Boehringer argued that their exclusivity should expire one year after its first commercial marketing date, as per 351(k)(6)(A).

FDA's memorandum in response stated that FDA "declines to adopt either Pfizer's or Boehringer Ingelheim's proposed interpretation" [15]. FDA further noted that Boehringer Ingelheim qualified for FIE for each of the three different strengths of its Cyltezo, and that just one of those strengths had FIE that extended past the launch date that Cyltezo had settled on with Abbvie (viz., July 1, 2023). Per FDA, FIEs for two strengths of Cyltezo expired in April 2023, and a third FIE expired in September 2023. According to one observer, "the extensive details of

[14] "As an initial matter, Congress in drafting the statutory language in section 351(k)(6) does not seem to have explicitly accounted for the fact that some interchangeable products would first be licensed as biosimilar and later licensed as interchangeable products, with 351(l)(6) litigation occurring in the interim. Nevertheless, this is the case for Cyltezo" [15].

FDA's statutory and factual interpretations and reasoning are complex and will be analyzed closely by industry for clues as to how other FIE determinations may be made for other biosimilar products under varying fact patterns" [16].

In October 2023, FDA updated labeling recommendations for biosimilars and interchangeables to enhance clarity and consistency [17]. Where previously FDA recommended that the Highlights of Prescribing Information in product labeling include a "biosimilarity statement" or "interchangeability statement" describing the product's relationship to its RP, in October 2023, FDA recommended that the Highlights of Prescribing Information in product labeling should include a biosimilarity statement for all biosimilars regardless of whether the biosimilar is approved as interchangeable [17]. According to FDA, labeling information identifying that a product has been approved as interchangeable is not necessary for informing the safe and effective use of the product to prescribing health care professionals, who are the primary intended audience for product labels [17]. Further, including biosimilarity statements in the product labeling for both biosimilars and interchangeables avoids increased confusion when a single biosimilar application and associated labeling may refer to both biosimilar and interchangeable products at the same time [17].

In contrast to FDA, EMA has no separate "interchangeable" designation; biosimilar substitution by non-prescribers is a policy matter left to member states.[15] In 2022, responding to calls for clarification of their stance on interchangeability, EMA further articulated their views on interchangeability [18, 19, 20]. Summarizing EMA's position, Executive Director Emer Cooke stated, "EMA has approved 86 biosimilar medicines since 2006. These medicines have been thoroughly reviewed and monitored over the past 15 years and the experience from clinical practice has shown that in terms of efficacy, safety, and immunogenicity they are comparable to their RPs and are therefore interchangeable" [21].

2.3 Clinical Studies

As noted above (Section 1), the abbreviated BLA for a biosimilar or interchangeable requires data comparing the proposed product to the FDA-approved RP to demonstrate biosimilarity. The comparative data include detailed analytical (structural and functional) characterization and comparison of the products, an assessment of toxicity, and comparative clinical studies. Consequently, rather than generating the same full profile of nonclinical and clinical data as the RP, a sponsor that shows its proposed product is highly similar to and has no clinically meaningful differences from the FDA-approved RP may rely in part on FDA's previous determination of safety and effectiveness for the RP for approval. This generally means that biosimilar sponsors do not need to conduct as many expensive and lengthy clinical studies as RP sponsors. Specifically, the requirements to demonstrate biosimilarity to a RP include data from:

- Analytical studies demonstrating that the biological product is highly similar to the RP, notwithstanding minor differences in clinically inactive components;

[15] In a study of EU biosimilar uptake policies by Vogler et al. [44], the authors reported that only Denmark required that biosimilars be substituted for originator products. Czech Republic allows substitution but does not encourage it. In 2020, France's Social Insurance law abolished their mandated substitution rule. Thirteen countries do not allow non-prescriber substitution [44].

- An assessment of toxicity (which may rely on, or consist of, animal or clinical studies; and
- A clinical study or studies sufficient to demonstrate safety, purity, and potency of the proposed product in one or more appropriate conditions of use (e.g., indications) for which the RP is licensed.

The latter typically includes assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD) and may also include comparative efficacy studies [22].[16]

It is noteworthy that the utility of some biosimilar clinical studies is being examined as in vitro and analytical studies have advanced technologically. As experience with evaluation of biosimilars mounted, some researchers, stakeholders, and regulators considered that data from comparative efficacy studies were unlikely to provide evidence that ran counter to the evidence developed by analytical, in vitro, and PK studies. In their report of their 2020 meeting, WHO's ECBS stated that "Australia, Canada, Europe, and the USA had indicated the feasibility of reducing the regulatory burden associated with the approval of similar biological products. In particular, clinical data requirements could be reduced based on existing principles subject to new insights on the precise role of clinical safety and efficacy studies. However, any proposed reduction in clinical safety and efficacy requirements would inevitably require an increased emphasis on quality and in vitro functional and human pharmacokinetic data" [23].

Schiestl et al. [24] scrutinized the clinical studies supporting biosimilar approval in the EU and the United States through November 2019. They found that in 36 of 38 instances, the comparative efficacy studies confirmed similarity. Webster et al. [25] examined all biosimilar license applications and evaluations from 2006 to 2019 in the EU, United States, Canada, and Australia. They found that "…no biosimilar that has been found to be highly similar to its reference by both analytical and human PK studies has ever failed to be approved because it was found not to be clinically equivalent to its reference in a powered study. It must be concluded that powered efficacy studies of these biosimilar candidates are of questionable value because their outcomes as regards biosimilarity are not in doubt." Moreover, Kurki et al. [26] noted that, "reduction of clinical efficacy and safety data requirements will increase the relative emphasis on physicochemical, structural, and in vitro functional data. The manufacturers need to use state-of-the-art analytical methods and in vitro functional tests and robustly apply these for assessing similarity" [26].

Both FDA and EMA have said that full-scale comparative safety and efficacy studies may not be necessary for all biosimilars seeking agency approval.[17] Briefly, their reasoning is that the RP has already been shown to be safe and effective. Hence, if a biosimilar has been shown to be

[16] The information that may be needed is more likely to be driven by fundamental scientific characteristics of the RP rather than by the extent of comparative analytical, PK/PD data (which is always comprehensive). For example, if the RP is a well characterized, highly purified recombinant protein where critical quality attributes and structural-functional relationships are well known. Also, whether the therapeutic dose range of the RP is in the steep part of the dose-response curve or in the therapeutic plateau (which would not be sensitive to small differences between products).

[17] "FDA evaluates each proposed biosimilar individually and advises manufacturers on the scope and extent of testing needed to show biosimilarity" [2].

a virtual replica of the RP by highly sensitive analytical, in vitro, and PK studies, a comparative efficacy study is not sensitive to small differences and therefore may not be additionally informative. Meanwhile, some researchers suggest that CES for biosimilars place unnecessary burdens and risk on human subjects and that they potentially rob subjects from other clinical studies of higher importance [27].

Reducing the scale or frequency of CES would substantially affect the cost of bringing a biosimilar to market. A 2020 study of the 16 biosimilars approved by both FDA and EMA at the time of the study found that 22 phase 2 and 3 studies (i.e., comparative efficacy studies) had been performed for 15 biosimilars submitted to and approved by both agencies [28]. Only the biosimilar Udenyca (pegfilgrastim-cbqv) was not required to submit a phase 2 or 3 study by either FDA or EMA. The number of patients in these studies ranged from 170 to 1,227. For submissions to FDA that came after EMA approval, the median number of phase 2/3 subjects was 573 (IQR: 437–733); for those that pre-dated EMA approval, the median number of subjects was 587 (IQR: 508–644).[18]

Another study estimated the median number of patients enrolled, treatment durations, and CES costs for biosimilars approved by FDA from January 2010 through October 2019 at 538 patients (IQR: 372–644), 55 weeks (IQR: 46–78), and $27.6 million (IQR: $18.0–$36.7 million), respectively [29].

A recent publication by McKinsey and Company examined 234 biosimilar projects in the United States, EU, and Japan and estimated that phase 2/3 studies consumed 65 percent of spending from analytical characterization through approval [22]. These authors also stated, “Clinical studies account for more than half of both budgets and timelines.” Representatives of manufacturers that we have interviewed to date estimated CES costs comprise 50–67 percent of pre-approval development costs. This is broadly comparable to the estimates reported in recent studies for new drugs (small molecules and biologics combined) in which the share of CES costs are estimated to comprise 48–77 percent of pre-approval development costs [30].

2.4 Biosimilar Uptake in the United States and Europe

Biosimilar competition has the potential to lower overall health care spending and to broaden the availability of medications that can markedly improve or save the lives of many people. EMA and EU nations had several years’ head start in evaluating and approving biosimilars, and initial uptake of biosimilars lagged in the United States. Since then, however, some U.S. biosimilars have reached or exceeded 80 percent of the volume of quarterly sales of daily doses, notably those referencing Avastin (bevacizumab) and Herceptin (trastuzumab), which have four and five biosimilars in their markets, respectively [31]. Avastin biosimilars and their launch dates are: Mvasi (bevacizumab-awwb, July 2019), Zirabev (bevacizumab-bvzr, December 2019), Alymsys (bevacizumab-maly, October 2022), and Vegzelma (bevacizumab-adcd, April 2023) [32]. Herceptin biosimilars and their launch dates are: Herzuma (trastuzumab-pkrb, March 2020), Kanjinti (trastuzumab-anns, July 2019), Ogivri (trastuzumab-dkst, December

[18] For EMA studies, the respective figures were 537 (IQR: 304–601) and 587 (IQR: 508–702).

2019), Ontruzant (trastuzumab-dttb, April 2020), and Trazimera (trastuzumab-qyyp, February 2020) [33] [34, 35, 36, 37].

A recent analysis of the impact of biosimilar market entry on the cost of Humira (adalimumab) in 30 European countries demonstrated the impact that competition can have in reducing prices [38]. Humira biosimilars entered the European market starting in October 2018 and as of Moorkens' analysis in May 2019, Humira biosimilars were available in 24 of the 30 surveyed countries [38]. The Humira biosimilars available in at least one European country at the time were: Amgevita, Hyrimoz, Hulio, Imraldi, and Idacio [38]. Confidential rebates and discounts off Humira's list prices were common. List prices for Humira (a single 40 mg syringe or pen injection) before biosimilar competition ranged from €318 in the Veneto province of Italy to €955 in Germany. After biosimilars were introduced, Humira's list prices in those two countries fell to €160 and €572, respectively. Moorkens et al. [38] were able to obtain real prices paid for Humira in 11 countries. After biosimilar entry, actual costs paid for Humira were far below list price in six countries, ranging from €50 to €99 in Holland to €160 in Italy. In five other countries, actual costs for Humira were between €300 and €400 per 40 mg [38].

While Humira prices in Europe decreased after biosimilar market entry began in October 2018, Humira prices in the United States remained high until the first Humira biosimilar launched in 2023. The contrast in the price of Humira between Europe and the United States emphasizes the impact that competition from biosimilars can have in reducing prices. In the United States, where there were no Humira biosimilars on the market until Amjevita launched in January 2023, the average 2019 IQVIA National Sales Perspective (NSP) price[19] from manufacturers and wholesalers to retail and non-retail channels for a 40 mg Humira syringe or pen was $2,536 [39], equal to €2,264 at the average 2019 exchange rate (Table 2).[20] This figure does not include the markups applied by the retail and non-retail purchasers on their sales to insured patients (as well as to the uninsured) who pay cash prices. According to information from Drugs.com [40], the average retail price for a 40 mg Humira syringe kit unit is around $3,650 for cash buyers in the United States, as of November 2023.

Table 2. Average IQVIA NSP Prices Per Prescription for Humira Sold in the United States from Manufacturers and Wholesalers to Retail and Non-retail Channels, 2019

11-Digit NDC	Type	Package Information	Price per Prescribed Unit [a]
00074006702	KIT	SYRINGE 40-80MG STRT 1X2	$3,518
00074024302	KIT	SYRINGE 40MG/0.4ML 1X2	$2,536
00074055402	PEN	IJ KIT 40MG/0.4ML 1X2	$2,418
00074153903	KIT	PEN IJ 80-40MG 1X3	$3,279
00074379902	KIT	40MG/0.8ML 1X2	$2,199
00074379903	KIT	SYRINGE 40MG/0.8ML 1X3	$2,602
00074379906	KIT	SYRINGE 40MG/0.8ML 1X6	$2,554

[19] IQVIA's NSP provides unit volumes and acquisition prices for drug shipments across all distribution channels.

[20] Humira prices increased after 2019. A search of drugpatentwatch.com indicated that the cost for one 40 mg unit in the last three NDCs in the table (00074433902, 00074433906, 00074433907) had risen by about 50 percent by Jan. 3, 2023, to $3,364–$3,369. In May 2021, the Drug Pricing Investigation Staff Report of the U.S. House Committee on Oversight and Reform stated that "A 40-milligram syringe of Humira is now priced at $2,984, or $77,586 annually—a 470 percent increase from the drug's launch [in 2002]."

11-Digit NDC	Type	Package Information	Price per Prescribed Unit [a]
00074433902	PEN	IJ KIT 40MG/0.8ML 1X2	$2,175
00074433906	KIT	PEN IJ 40MG/0.8ML 1X6	$2,008
00074433907	KIT	PEN IJ 40MG/0.8ML 1X4	$2,250

[a] Total 2019 NSP sales divided by total 2019 NSP extended units sold.

European health care systems combine several methods to lower the costs of biologics and to encourage biosimilar uptake. Brief descriptions of some of these methods follow. In Europe, many governments have adopted a range of direct tactics to increase the uptake of biosimilars. Shared benefit programs, tendering, prescription quotas, price linkage, reference pricing, international nonproprietary name (INN) prescribing, best value prescribing, and biosimilar substitution—these are all practiced to varying extents across the EU and the United Kingdom. Several of these policies, described below, have analogs in the United States. In the *Comprehensive Plan for Addressing High Drug Prices*, ASPE notes several policies in effect in different corners of the U.S. healthcare system that resemble the EU policies described below [41].

***Shared benefit programs*.** The national health insurer rewards prescribers who prescribe biosimilars by providing their hospital, department, or clinic with a percentage of the funds saved or a fixed amount. In France, for each unit prescribed, the benefit is 20 percent of the cost differential. A pilot program at 62 French hospitals offers a 30 percent return; unsurprisingly, the pilot hospitals' biosimilar uptake was 9 percent higher. In Ireland, biosimilar uptake was lagging until the national Health Service Executive (HSE) initiated a best value biologic program and paid €500 per patient for those that were initiated to or switched to the best value biosimilar. In 12 months, biosimilar uptake rose to 50 percent [42].

Tendering. Tendering allows institutions to publicly offer contracts for drug supplies at specific prices and allows manufacturers to compete for them. This is a common approach in European nations and can result in steep discounts owing to intense competition and encouragement from national insurers. In the Netherlands, for example, the reimbursement limit for Humira even before biosimilar competition was about €100—80 percent below list price. Hospitals were encouraged to make up the difference through negotiation [38]. This approach is like that of the Veterans Affairs' (VA's) national contracts program, which, through negotiation, results in prices lower than Federal Supply Schedule (FSS) contracts and is used for VA's standardization efforts. A similar system is also being implemented for Medicare under the new Inflation Reduction Act provisions.

Price linkage. This practice mandates that the first biosimilar in a market must be priced some fixed percentage lower than the RP; 30 percent lower is a common figure; in France and Austria, first biosimilars must be priced at 40 and 38 percent below the reference price, respectively. Often, subsequent biosimilar entries must be lower still. Some countries also link the RP to the biosimilar, i.e., the reference cannot be priced higher than the biosimilar or must lower its own price by a fixed percentage. Eleven countries have some form of price linkage.

In the United States, analogous cost controls could be implemented in Medicare Part D by placing biosimilar products on preferred formulary tiers that require lower copays than do the tiers that brand drugs and RPs occupy [43]. Another option for Medicare Part B would be to

have a single payment limit applicable to the RP and the biosimilar product(s) of that RP, which could spur price competition and drive down average sales prices for all products included in the payment limit calculation, as is done for small molecule drugs and their generics [43].

INN prescribing. In four countries, prescribers must use the INN of the original biologic when prescribing for naïve patients; in six countries, INN prescribing is voluntary but recommended. INN prescriptions are not allowed in three countries, and in three others the pharmacist must call the prescriber before filling an INN prescription [44]. INN prescribing has much the same effect as allowing pharmacists to substitute an interchangeable for an RP. There is no U.S. analog for this policy.

2.5 Current CDER-Approved Biosimilars and Interchangeables

FDA's Purple Book: Database of Licensed Biological Products provides a compendium of licensed biological products regulated by CDER and CBER. The Purple Book includes approved BLAs, including supplement approvals that result in a new line listing such as a newly approved strength or route of administration. Table 3 presents the filters we applied to eliminate entries from September 2024 Purple Book data download that are not applicable to analyzing sales data from IQVIA NSP, given the scope of our study and our modeling of biosimilar/interchangeable market entry decisions.

Table 3. FDA-approved Entries in September 2024 Purple Book: Steps to Obtain List of Unique Original Biologic and Biosimilar Product Names

Category	Approval Pathway		Total
	351(a) Original Biologics	351(k) Biosimilars/ Interchangeables	
Total CDER-Approved BLAs, including Supplements	857	153	1,010
BLA Type = "Supplement" or Blank	–278	–41	-319
Licensure = "Voluntarily Revoked"	–71	0	-71
Marketing Status = "Disc"	–102	–7 [a]	-109
Marketing Status = "OTC"	–9	0	-9
TOTAL IN SCOPE	397	105	502
Duplicate Proprietary Names	–138	–48	-186
Total In-scope Molecule Names	259	57 [b]	316

CDER = FDA's Center for Drug Evaluation and Research
BLA = Biologics license application
Disc = Discontinued
OTC = Over the counter
[a] Discontinued biosimilars include the following approved biosimilars, two of which are likely to enter their market in 2029: (1) Eticovo (etanercept-ykro) and Erelzi (etanercept-szzs) are barred by court order from marketing until 2029 when Enbrel patent expires, (2) Ixifi (infliximab-qbtx), which Pfizer withdrew from the U.S. market after acquiring it as part of a corporate acquisition. We include these three approved biosimilars in other tables and data summaries representing all CDER-approved biosimilars.
[b] These 57 biosimilars are distributed across 16 RP markets. The Purple Book has separate entries for Jubbonti/Wyost (denosumab-bbdd), which are the interchangeables for the RP Prolia/Xgeva (denosumab). We therefore counted them separately for this summary table. But, in keeping with FDA's practice elsewhere, we list and count Jubbonti/Wyost (and Prolia/Xgeva) as one biosimilar (and one RP) elsewhere in this report.

Overall, there were 1,010 CDER-approved entries listed in the Purple Book; 153 of these were original BLAs or supplements submitted under the 351(k) approval pathway established for biosimilars under the BPCIA. The remaining 857 CDER-approved entries submitted 351(a) original or supplemental applications.[21] One of the differences between the generic drug and the biosimilar environments is that nearly all biosimilar manufacturers have provided their products with a unique trademark or brand name (e.g., Amjevita), while generic manufacturers generally do not. Table 4 lists the 17 original biologics that have been referenced by biosimilars approved by FDA to enter the commercial market. The right-hand column indicates whether the product is mainly purchased by the patient in a retail setting and self-administered or is supplied and administered to the patient by a medical provider in a clinic or other medical setting.

Table 4. Treatment Duration and Function for 17 Reference Products (RPs) with 63 Approved Biosimilars in the United States, January 2015–December 2024

Reference Product (RP)	Number of Approved Biosimilars	Treatment Duration	Therapeutic Area	Primary Purchase Location
Actemra (tocilizumab)	2	Long term	Immunosuppression	Retail
Avastin (bevacizumab)	5	Short term	Oncology	Medical setting
Enbrel (etanercept)	2	Long term	Immunosuppression	Retail
Epogen (epoetin-alfa)	1	Short term	Oncology support	Medical setting
Eylea (aflibercept)	5	Long term	Ophthalmology (anti-angiogenic)	Medical setting
Herceptin (trastuzumab)	6	Short term	Oncology	Medical setting
Humira (adalimumab)	10	Long term	Immunosuppression	Retail
Lantus (Insulin glargine)	2	Long term	Diabetes	Retail
Lucentis (ranibizumab)	2	Long term	Ophthalmology (anti-angiogenic)	Medical setting
Neulasta (pegfilgrastim)	6	Short term	Oncology support (neutropenia)	Medical setting
Neupogen (filgrastim)	4	Short term	Oncology support (neutropenia)	Medical setting
Prolia/Xgeva (denosumab)	1 [a]	Long term	Osteoporosis	Medical setting
Remicade (infliximab)	4	Long term	Immunosuppression	Medical setting
Rituxan (rituximab)	3	Short or long term	Oncology	Medical setting
Soliris (eculizumab)	2	Long term	Immunosuppression	Medical setting
Stelara (ustekinumab)	7	Long term	Immunosuppression	Retail
Tysabri (natalizumab)	1	Long term	Immunosuppression	Medical setting
Total	**63**	**n/a**	**n/a**	**n/a**

[a] The RPs Prolia and Xgeva are proprietary names for the same molecule, denosumab, and are often combined by FDA, as in Prolia/Xgeva. This also happens with their biosimilars, Jubbonti and Wyost. Treating Jubbonti/Wyost as one biosimilar gives a total of 63 approved biosimilars.

Table 5 presents the 63 biosimilars approved by CDER to date, including the approval dates of the biosimilars and their RPs. The right-most column presents the calculated intervals between each RP's approval and the first biosimilar's launch. This interval is a fair representation of the time in the market that the RP has been free of biosimilar competition. This gap ranged from 14.3 years (Actemra) to 29.4 years (Neupogen). The median gap and the

[21] Biologic companies frequently submit several supplemental or original BLAs for different dosages, dilutions, or delivery methods of a single product. Humira, for instance, has 8 supplemental and one original BLAs. This is why a total of 1,010 supplemental and original BLAs represent 316 differently-named original biologics and biosimilars.

average gap were both 20.8 years, and the interquartile range was 19.1 years to 22.2 years. Because RP companies often apply for patents years before submitting their BLAs, these intervals of de facto monopoly exceed both the 12 years of post-approval exclusivity granted to original biologics under the BPCIA and the years of protection provided by the RP company's initial patents—which, as mentioned, are usually granted several years before an original biologic's approval and market entry. These lengthy periods of monopoly may result from follow-on patents or other strategies that RP companies sometimes implement to delay biosimilar market entry. The longer lag times for earlier biosimilars may also be related to the lack of an established biosimilar pathway at that time. For example, Zarxio (filgrastim-sndz) is one of the earliest biosimilars of Neupogen (filgrastim) launched in the U.S. market and the length of time Neupogen (filgrastim) was free of market competition was 24.9 years; higher than the median of 20.8 years. In contrast, this gap appears to be significantly shorter for some of the more recent biosimilar launches, such as for Tyenne (tocilizumab-aazg), a biosimilar of Actemra (tocilizumab) with 14.3 years—around 43 percent shorter than that of Zarxio (filgrastim-sndz).

Table 6 presents the dates when reference product companies (RPCs) first filed patent-related court actions against some of the 44 biosimilars that had been approved as of November 2023. As is discussed in detail in Section 6.1.2, the biosimilar company could have notified the RPC that they intended to market their biosimilar product commercially. Biosimilar companies normally do this when they file their abbreviated BLA with CDER, though they can do so before, if they choose.

Table 5. Sixty-three Biosimilars and Interchangeables Approved by FDA, March 6, 2015–Dec. 20, 2024, their Reference Products (RPs), CDER Approval Dates, and U.S. Marketing Launch Dates

RP Name RP Proper Name RP Manufacturer	Type or Therapeutic Area	RP Approval Date	Indications Treated	Biosimilar Name Biosimilar Proper Name	Listed Biosimilar Manufacturer(s)	Biosimilar Approval Date	Biosimilar U.S. Launch Date *(projected date)*	Months from Biosimilar Approval to Biosimilar Market Launch	Months from RP Approval to Biosimilar Market Launch (Years)
ACTEMRA tocilizumab Genentech	Monoclonal Antibody Interleukin Inhibitor Immunosuppression	1/8/2010	Autoimmune diseases e.g., rheumatoid arthritis	TOFIDENCE tocilizumab-bavi	Biogen	9/29/2023	Not Launched	n/a	n/a
				TYENNE tocilizumab-aazg	Fresenius Kabi	3/5/2024	4/1/2024	0.9	**171.3 (14.3)**
AVASTIN bevacizumab Genentech	Monoclonal Antibody - VEGF Inhibitor	2/26/2004	Cancer treatment anti-angiogenesis for various cancers	MVASI bevacizumab-awwb	Amgen	9/14/2017	7/19/2019	22.4	**184.3 (15.4)**
				ZIRABEV bevacizumab-bvzr	Pfizer	6/27/2019	1/3/2020	6.3	189.8 (15.8)
				ALYMSYS bevacizumab-maly	Amneal	4/13/2022	10/3/2022	5.8	222.8 (18.6)
				VEGZELMA bevacizumab-adcd	Celltrion	9/27/2022	4/1/2023	6.2	228.7 (19.1)
				AVZIVI bevacizumab-tnjn	Bio-Thera/ Sandoz	12/6/2023	12/6/2023	0.03	236.0 (19.7)
ENBREL etanercept Immunex	Receptor Fusion Protein - TNF Inhibitor	11/2/1998	Autoimmune diseases e.g., rheumatoid arthritis, plaque psoriasis	ERELZI etanercept-szzs	Sandoz	8/30/2016	(*1/1/2029*) [a]	n/a	n/a [min. 361 months, or 30.1 years]
				ETICOVO etanercept-ykro	Samsung	4/25/2019	(*1/1/2029*)[a]	n/a	n/a [min. 361 months, or 30.1 years]
EPOGEN/PROCRIT erythropoietin alpha Amgen	Erythropoiesis-stimulating Agent Hematology Oncology support	6/1/1989	Anemia especially in chronic kidney disease and chemotherapy	RETACRIT epoetin alfa-epbx	Hospira Pfizer	5/15/2018	11/1/2018	5.7	**352.3 (29.4)**
EYLEA Aflibercept Regeneron	Recombinant fusion protein; Vascular endothelial growth factor (VEGF) inhibitor	11/18/2011	Wet macular degeneration	**YESAFILI** **aflibercept-jbvf**	Viatris	5/20/2024	Not yet launched	n/a	n/a
				AHZANTIVE aflibercept-mrbb	Formycon AG	6/28/2024	Not yet launched	n/a	n/a
				OPUVIZ **aflibercept-yszy**	Samsung Bioepis	5/20/2024	Not yet launched	n/a	n/a

RP Name RP Proper Name RP Manufacturer	Type or Therapeutic Area	RP Approval Date	Indications Treated	Biosimilar Name Biosimilar Proper Name	Listed Biosimilar Manufacturer(s)	Biosimilar Approval Date	Biosimilar U.S. Launch Date *(projected date)*	Months from Biosimilar Approval to Biosimilar Market Launch	Months from RP Approval to Biosimilar Market Launch (Years)
	Ophthalmology			**ENZEEVU aflibercept-abzv**	Sandoz	8/9/2024	Not yet launched	n/a	n/a
				PAVBLU aflibercept-ayyh	Amgen	8/23/2024	Not yet launched	n/a	n/a
HERCEPTIN trastuzumab Genentech	Monoclonal Antibody Oncology	9/25/1998-HER2+ metastatic breast cancer. 2006 - HER2+ early breast cancer 2010 = HER2+ metastatic stomach cancer.	Oncology HER2-positive breast and stomach cancer	KANJINTI trastuzumab-anns	Amgen	6/13/2019	7/1/2019	0.6	**252.8 (21.1)**
				OGIVRI trastuzumab-dkst	Biocon	12/1/2017	12/1/2019	24.3	257.9 (21.5)
				TRAZIMERA trastuzumab-qyyp	Pfizer	3/11/2019	2/1/2020	10.9	260.0 (21.7)
				HERZUMA trastuzumab-pkrb	Celltrion	12/14/2018	3/1/2020	14.8	260.9 (21.7)
				ONTRUZANT trastuzumab-dttb	Samsung	1/18/2019	4/1/2020	14.6	262.0 (21.8)
				HERCESSI trastuzamab-strf	Accord Biopharma	4/25/2024	4/25/2024	0.03	311.5 (26.0)
HUMIRA adalimumab AbbVie	Monoclonal Antibody - TNF Inhibitor	12/31/2002	Autoimmune diseases e.g., rheumatoid arthritis, psoriatic arthritis	**AMJEVITA Adalimumab -atto**	Amgen	9/23/2016	1/31/2023	71.2	**244.5 (20.4)**
				CYLTEZO adalimumab-adbm	Boehringer Ingelheim	8/25/2017	7/1/2023	71.2	249.6 (20.8)
				HADLIMA adalimumab-bwwd	Samsung	7/23/2019	7/1/2023	48.0	249.6 (20.8)
				IDACIO adalimumab-aacf	Fresenius Kabi	12/13/2022	7/1/2023	6.7	249.6 (20.8)
				YUFLYMA adalimumab-aaty	Celltrion	5/23/2023	7/2/2023	1.3	249.6 (20.8)
				YUSIMRY adalimumab-aqvh	Coherus BioSciences	12/17/2021	7/3/2023	18.8	249.6 (20.8)
				HULIO adalimumab-fkjp	Mylan	7/6/2020	7/31/2023	37.3	250.6 (20.9)
				HYRIMOZ adalimumab-adaz	Sandoz	10/30/2018	9/30/2023	59.9	252.6 (21.1)

RP Name RP Proper Name RP Manufacturer	Type or Therapeutic Area	RP Approval Date	Indications Treated	Biosimilar Name Biosimilar Proper Name	Listed Biosimilar Manufacturer(s)	Biosimilar Approval Date	Biosimilar U.S. Launch Date *(projected date)*	Months from Biosimilar Approval to Biosimilar Market Launch	Months from RP Approval to Biosimilar Market Launch (Years)
				ABRILADA **adalimumab-afzb**	Pfizer	11/15/2019	11/20/2023	48.9	254.3 (21.2)
				SIMLANDI **Adalimumab-ryvk**	Alvotech/Teva	2/24/2024	5/20/2024	2.2	259.7 (21.6)
LANTUS Insulin glargine Sanofi-Aventis	Insulin	04/20/2000	Diabetes management long-acting insulin	**SEMGLEE** **insulin glargine-yfgn**	Biocon	7/28/2021	11/16/2021	3.7	**263.3** **(21.9)**
				REZVOGLAR [b] **insulin glargine-aglr**	Eli Lilly	12/17/2021	4/1/2023	15.7	280.0 (23.3)
LUCENTIS ranibizumab Genentech	Monoclonal Antibody - VEGF-A Inhibitor	06/30/2006	Ophthalmology e.g., wet age-related macular degeneration	**BYOOVIZ** **ranibizumab-nuna**	Samsung	9/17/2021	6/1/2022	8.6	**190.7** **(15.9)**
				CIMERLI **ranibizumab-eqrn**	Coherus BioSciences	8/2/2022	10/3/2022	2.1	194.7 (16.2)
NEULASTA pegfilgrastim Amgen	Granulocyte Colony-stimulating Factor	1/31/2002	Increase white blood cell counts chemotherapy-induced neutropenia	FULPHILA pegfilgrastim-jmdb	Biocon	6/4/2018	7/30/2018	1.9	**200.8** **(16.7)**
				UDENYCA pegfilgrastim-cbqv	Coherus BioSciences	11/2/2018	1/1/2019	2.0	206.0 (17.2)
				ZIEXTENZO pegfilgrastim-bmez	Sandoz	11/4/2019	12/1/2019	0.9	217.1 (18.1)
				NYVEPRIA pegfilgrastim-apgf	Hospira Pfizer	6/10/2020	12/1/2020	5.8	229.3 (19.1)
				STIMUFEND pegfilgrastim-fpgk	Fresenius Kabi	9/1/2022	2/1/2023	5.1	255.7 (21.3)
				FYLNETRA pegfilgrastim-pbbk	Kashiv BioSciences	5/26/2022	5/1/2023	11.3	258.7 (21.6)
NEUPOGEN filgrastim Amgen	Granulocyte Colony-stimulating Factor	2/20/1991	Increase white blood cell counts chemotherapy-induced neutropenia	ZARXIO filgrastim-sndz	Sandoz	3/6/2015	9/3/2015	6.0	**298.7** **(24.9)**
				NIVESTYM filgrastim-aafi	Hospira Pfizer	7/20/2018	10/1/2018	2.4	336.2 (28.0)
				RELEUKO filgrastim-ayow	Kashiv BioSciences	2/25/2022	11/22/2022	9.0	386.6 (32.2)

RP Name RP Proper Name RP Manufacturer	Type or Therapeutic Area	RP Approval Date	Indications Treated	Biosimilar Name Biosimilar Proper Name	Listed Biosimilar Manufacturer(s)	Biosimilar Approval Date	Biosimilar U.S. Launch Date *(projected date)*	Months from Biosimilar Approval to Biosimilar Market Launch	Months from RP Approval to Biosimilar Market Launch (Years)
				NYPOZI filgrastim-txid	Tanvex BioPharma USA	6/28/2024	*(pending)*	n/a	n/a
PROLIA/XGEVA Denosumab Amgen/GSK	Monoclonal antibody	6/1/2010	Osteoporosis after menopause and in Men. Bone loss induced by breast cancer and prostate cancer Treatments	**JUBBONTI/WYOST denosumab-bbdz**	Sandoz	3/5/2024	*(2/19/2025)* [c]	11.7	**179.2 (14.9)**
REMICADE infliximab Janssen Biotech	Monoclonal Antibody - TNF Inhibitor Immunology	8/24/1998	Autoimmune and inflammatory conditions e.g., Crohn's disease	INFLECTRA infliximab-dyyb	Celltrion & Pfizer	4/5/2016	11/30/2016	8.0	**222.4 (18.5)**
				RENFLEXIS infliximab-abda	Samsung & Organon	4/21/2017	7/24/2017	3.1	230.3 (19.2)
				AVSOLA infliximab-axxq	Amgen	12/6/2019	7/1/2020	6.9	266.1 (22.2)
				IXIFI [d] infliximab-qbtx	Pfizer	12/13/2017	Not Launched	n/a	n/a
RITUXAN rituximab Genentech	Monoclonal Antibody - B-cell Inhibitor	11/26/1997	Oncology and autoimmune disorders e.g., non-Hodgkin lymphoma, RA	TRUXIMA rituximab-abbs	Celltrion	11/28/2018	11/11/2019	11.6	**267.3 (22.3)**
				RUXIENCE rituximab-pvvr	Pfizer	7/23/2019	2/1/2020	6.4	270.1 (22.5)
				RIABNI rituximab-arrx	Amgen	12/17/2020	1/1/2021	0.5	281.2 (23.4)
SOLIRIS Eculizumab Alexion	Monoclonal antibody--Immunosuppressive	3/16/2007	Paroxysmal nocturnal hemoglobinuria (PNH); atypical hemolytic uremic e (aHUS).	**BKEMV eculizumab-aeeb**	Amgen	5/28/2024	*3/1/2025 [c]*	9.2	**218.6 (18.2)**
				EPYSQLI Eculizumab-aagh	Samsung Bioepis	7/19/2024	*3/1/2025 [c]*	7.5	218.6 (18.2)
STELARA ustekinumab	Monoclonal Antibody - Interleukin Inhibitor	9/25/2009	Autoimmune diseases e.g.,	**WEZLANA ustekinumab-auub**	Amgen	10/31/2023	*1/1/2025 [c]*	14.3	**185.9 (15.5)**

RP Name RP Proper Name RP Manufacturer	Type or Therapeutic Area	RP Approval Date	Indications Treated	Biosimilar Name Biosimilar Proper Name	Listed Biosimilar Manufacturer(s)	Biosimilar Approval Date	Biosimilar U.S. Launch Date *(projected date)*	Months from Biosimilar Approval to Biosimilar Market Launch	Months from RP Approval to Biosimilar Market Launch (Years)
Janssen Biotech			plaque psoriasis, Crohn's disease	SELARSDI ustekinumab-aekn	Alvotech/Teva	4/16/2024	*2/21/2025 [c]*	10.4	187.6 (15.6)
				PYZCHIVA **ustekinumab-ttwe**	Samsung Bioepis	6/28/2024	*(2/21/2025) [c]*	7.9	187.6 (15.6)
				OTULFI ustekinumab-aauz	Formycon/Fresenius Kabi	10/8/2024	*(2/21/2025) [c]*	4.5	187.6 (15.6)
				STEQEYMA (Ustekinumab-stba)	Celltrion	12/20/2024	*(2025)*	N/A	>187.6 (15.6)
				YESINTEK (ustekinumab-kfce)	Biocon	12/01/2024	*(2/22/2025)*	2.6	187.6 (15.6)
				IMULDOSA (ustekinumab-srlf)	Accord Biopharma	10/24/2024	*2025*	N/A	>187.6 (15.6)
TYSABRI natalizumab Biocon	Monoclonal Antibody - T-cell Inhibitor	11/23/2004	Multiple sclerosis and Crohn's disease	TYRUKO natalizumab-sztn	Sandoz	8/24/2023	Not Launched	n/a	n/a
XGEVA denosumab Amgen	Monoclonal antibody	11/18/2010	Disease-related bone loss and calcium deficiency	**WYOST** **denosumab-bbdz**	Sandoz	3/5/2024	*(2/19/2025) [c]*	11.7	**173.6** **(14.5)**

n/a = not applicable
RP = reference product
BOLD font indicates biosimilar has interchangeable designation.
RED font indicates the number of months from reference product approval to launch of first biosimilar competitor.
[a] Due to adverse IP litigation outcomes, Erelzi and Eticovo may not enter their market until 2029 [45]. Eticovo's status is listed as "Disc" in the Purple Book.
[b] Rezvoglar was approved as a biosimilar on 12/17/2021 and as an interchangeable 11/16/2022.
[c] The listed date is an estimated or projected future launch date.
[d] Ixifi's status is listed as "Disc" in the Purple Book. After a corporate acquisition gave them rights to another infliximab biosimilar, Pfizer said they "had no plans" to market Ixifi in the United States.

Table 6. Dates of and Intervals between Approval, Launch, and Litigation Filings for 44 Biosimilars Approved as of November 2023

RP RP Proper Name RP Manufacturer	Type	Biosimilar Name Biosimilar Proper Name	Listed Biosimilar Manufacturer(s)	Biosimilar Approval Date	Biosimilar U.S. Launch Date	Date Litigation filed by RP	Months from Litigation Filing by RP to Biosimilar Launch	IP Litigation Outcome
ACTEMRA tocilizumab Genentech	Monoclonal Antibody - Interleukin Inhibitor	TOFIDENCE tocilizumab-bavi	Biogen	9/29/2023	Not Launched	7/13/2023	NA	Settlement
AVASTIN bevacizumab Genentech	Monoclonal Antibody - VEGF Inhibitor	MVASI bevacizumab-awwb	Amgen	9/14/2017	7/19/2019	10/6/2017	21.3	Settlement
		ZIRABEV bevacizumab-bvzr	Pfizer	6/27/2019	1/3/2020	4/5/2019	9.0	Settlement
		ALYMSYS bevacizumab-maly	Amneal	4/13/2022	10/3/2022		No Litigation Filed	
		VEGZELMA bevacizumab-adcd	Celltrion	9/27/2022	4/1/2023		No Litigation Filed	
ENBREL etanercept Immunex	Receptor Fusion Protein - TNF Inhibitor	ERELZI etanercept-szzs	Sandoz	8/30/2016	1/1/2029 [a]	2/26/2016		Infringement
		ETICOVO etanercept-ykro	Samsung	4/25/2019	1/1/2029 [a]	4/29/2019		Permanent Injunction
EPOGEN erythropoietin alpha Amgen	Erythropoiesis-stimulating Agent	RETACRIT epoetin alfa-epbx	Hospira Pfizer	5/15/2018	11/1/2018	9/18/2015	37.4	Infringement
HERCEPTIN trastuzumab Genentech	Monoclonal Antibody	KANJINTI trastuzumab-anns	Amgen	6/13/2019	7/1/2019	6/21/2018	12.3	Settlement
		OGIVRI trastuzumab-dkst	Biocon	12/1/2017	12/1/2019		No Litigation Filed	
		TRAZIMERA trastuzumab-qyyp	Pfizer	3/11/2019	2/1/2020	11/17/2017	26.4	Settlement
		HERZUMA trastuzumab-pkrb	Celltrion	12/14/2018	3/1/2020	1/12/2018	25.5	Settlement
		ONTRUZANT trastuzumab-dttb	Samsung	1/18/2019	4/1/2020	9/4/2018	18.9	Settlement
HUMIRA adalimumab AbbVie	Monoclonal Antibody - TNF Inhibitor	AMJEVITA Adalimumab -atto	Amgen	9/23/2016	1/31/2023	8/4/2016	77.7	Settlement
		CYLTEZO adalimumab-adbm	Boehringer Ingelheim	8/25/2017	7/1/2023	8/2/2017	70.8	Settlement

RP RP Proper Name RP Manufacturer	Type	Biosimilar Name Biosimilar Proper Name	Listed Biosimilar Manufacturer(s)	Biosimilar Approval Date	Biosimilar U.S. Launch Date	Date Litigation filed by RP	Months from Litigation Filing by RP to Biosimilar Launch	IP Litigation Outcome
		HADLIMA adalimumab-bwwd	Samsung	7/23/2019	7/1/2023		No Litigation Filed	
		IDACIO adalimumab-aacf	Fresenius Kabi	12/13/2022	7/1/2023		No Litigation Filed	
		YUFLYMA adalimumab-aaty	Celltrion	5/23/2023	7/2/2023		No Litigation Filed	
		YUSIMRY adalimumab-aqvh	Coherus BioSciences	12/17/2021	7/3/2023		No Litigation Filed	
		HULIO adalimumab-fkjp	Mylan	7/6/2020	7/31/2023		No Litigation Filed	
		HYRIMOZ adalimumab-adaz	Sandoz	10/30/2018	9/30/2023	8/10/2018	61.5	Settlement
		ABRILADA [b] adalimumab-afzb	Pfizer	11/15/2019	11/20/2023		Settled	
LANTUS Insulin glargine Sanofi-Aventis	Insulin	SEMGLEE [c] insulin glargine-yfgn	Biocon	7/28/2021	11/16/2021		No Litigation Filed	
		REZVOGLAR insulin glargine-aglr	Eli Lilly	12/17/2021	4/1/2023		No Litigation Filed	
LUCENTIS ranibizumab Genentech	Monoclonal Antibody - VEGF-A Inhibitor	BYOOVIZ ranibizumab-nuna	Samsung	9/17/2021	6/1/2022		No Litigation Filed	
		CIMERLI ranibizumab-eqrn	Coherus BioSciences	8/2/2022	10/3/2022		No Litigation Filed	
NEULASTA pegfilgrastim Amgen	Granulocyte Colony-stimulating Factor	FULPHILA pegfilgrastim-jmdb	Biocon	6/4/2018	7/30/2018	9/22/2017	10.2	Non-infringement
		UDENYCA pegfilgrastim-cbqv	Coherus BioSciences	11/2/2018	1/1/2019	5/10/2017	19.7	Dismissed
		ZIEXTENZO pegfilgrastim-bmez	Sandoz	11/4/2019	12/1/2019	3/4/2016	44.8	Non-infringement
		NYVEPRIA pegfilgrastim-apgf	Hospira Pfizer	6/10/2020	12/1/2020	2/11/2020	9.6	Settlement
		STIMUFEND pegfilgrastim-fpgk	Fresenius Kabi	9/1/2022	2/1/2023		No Litigation Filed	
		FYLNETRA	Kashiv BioSciences	5/26/2022	5/1/2023		No Litigation Filed	

RP RP Proper Name RP Manufacturer	Type	Biosimilar Name Biosimilar Proper Name	Listed Biosimilar Manufacturer(s)	Biosimilar Approval Date	Biosimilar U.S. Launch Date	Date Litigation filed by RP	Months from Litigation Filing by RP to Biosimilar Launch	IP Litigation Outcome
		pegfilgrastim-pbbk						
NEUPOGEN filgrastim Amgen	Granulocyte Colony-stimulating Factor	ZARXIO filgrastim-sndz	Sandoz	3/6/2015	9/3/2015	10/24/2014	10.3	Non-infringement
		NIVESTYM filgrastim-aafi	Hospira Pfizer	7/20/2018	10/1/2018	7/18/2018	2.5	Dismissed
		Nypozi filgrastim-txid	Tanvex BioPharma USA					
		RELEUKO filgrastim-ayow	Kashiv BioSciences	2/25/2022	11/22/2022		No Litigation Filed	
REMICADE infliximab Janssen Biotech	Monoclonal Antibody - TNF Inhibitor	INFLECTRA infliximab-dyyb	Celltrion & Pfizer	4/5/2016	11/30/2016	3/6/2015	20.8	Non-infringement & Invalidity
		RENFLEXIS infliximab-abda	Samsung & Organon	4/21/2017	7/24/2017	5/17/2017	2.2	Dismissed
		AVSOLA infliximab-axxq	Amgen	12/6/2019	7/1/2020		No Litigation Filed	
		IXIFI infliximab-qbtx	Pfizer	12/13/2017	Not Launched		No Litigation Filed	
RITUXAN rituximab Genentech	Monoclonal Antibody - B-cell Inhibitor	TRUXIMA rituximab-abbs	Celltrion	11/28/2018	11/11/2019	1/12/2018	21.9	Settlement
		RUXIENCE rituximab-pvvr	Pfizer	7/23/2019	2/1/2020		No Litigation Filed	
		RIABNI rituximab-arrx	Amgen	12/17/2020	1/1/2021		No Litigation Filed	
STELARA ustekinumab Janssen Biotech	Monoclonal Antibody - Interleukin Inhibitor	WEZLANA [d] ustekinumab-auub	Amgen	10/31/2023	1/1/2025	11/29/2022		Pending

RP = reference product; IP = intellectual property

[a] The listed date is an estimated or projected future launch date.

[b] Launch dates for Humira biosimilars were established in settlement of IP litigation with Abbvie. Abrilada was approved as biosimilar in November 2019 and as interchangeable in October 2023, prior to the agreed-upon launch date.

[c] Biosimilar Semglee was approved June 11, 2020 and launched in August 2020. The biosimilar Semglee was to be withdrawn by end of 2021 in favor of the interchangeable product.

[d] Amgen's settlement agreement with J&J calls for a launch date “no later than January 1, 2025.” (Brittain 2023) https://www.reuters.com/business/healthcare-pharmaceuticals/amgen-settles-jj-patent-lawsuit-over-drug-similar-blockbuster-stelara-2023-05-23/

IQVIA NSP provides invoice sales not inclusive of rebates and discounts, which offers insight and preliminary data regarding market penetration of biosimilars. Table 7 lists the 28 biosimilars marketed through the end of 2023 and includes the total sales for each. In 2021, 20 biosimilars from seven companies were marketed throughout the year. Biosimilar sales for those companies totaled $6.9 billion. In 2022, sales were reported for 10 companies marketing 28 biosimilar products in the United States. As of 2023, there were 13 companies making 47 biosimilar products, which correspond to 10 different biologic molecules. These biosimilars earned $7.7 billion in invoice sales in 2023. Table 7 shows the biosimilar product sales by sponsor, and Table 8 compares dollar sales of biosimilars with sales of RPs, aggregated by the molecule's proper name.

Table 7. IQVIA NSP Sales in CY 2023 for 47 Biosimilars Marketed in the United States by 13 Companies

Biosimilar Sponsor	Proper Name of Molecule	Biosimilar Brand Name (**Bold** = Interchangeable)	IQVIA NSP Sales, CY 2023 (Million 2023 $)
AMGEN CORPORATION	ADALIMUMAB	**AMJEVITA**	**$112.3**
	INFLIXIMAB	AVSOLA	$301.2
	TRASTUZUMAB	KANJINTI	$371.6
	BEVACIZUMAB	MVASI	$838.7
	RITUXIMAB	RIABNI	$137.1
AMNEAL INC	BEVACIZUMAB	ALYMSYS	$71.8
	PEGFILGRASTIM	FYLNETRA	$6.8
	FILGRASTIM	RELEUKO	$3.1
BIOCON CORP	ADALIMUMAB	ADALIMUMAB FKJP	$1.1
	ADALIMUMAB	HULIO	$0.2
	PEGFILGRASTIM	FULPHILA	$298.6
	INSULIN GLARGINE	INSULIN GLARG YFGN	$201.4
	TRASTUZUMAB	OGIVRI	$111.9
	INSULIN GLARGINE	**SEMGLEE**	**$378.4**
BIOGEN IDEC CORP	RANIBIZUMAB	**BYOOVIZ**	**$53.2**
BOEHRINGER INGEL	ADALIMUMAB	ADALIMUMAB ADBM	$0.1
	ADALIMUMAB	**CYLTEZO**	**$4.1**
	ADALIMUMAB	**CYLTEZO CROHNS**	**$0.3**
	ADALIMUMAB	**CYLTEZO PSORIASIS**	**$0.1**
CELLTRION USA	BEVACIZUMAB	VEGZELMA	$14.2
	ADALIMUMAB	YUFLYMA	$0.4
COHERUS BIOSCIENCE	PEGFILGRASTIM	UDENYCA	$252.3
	ADALIMUMAB	YUSIMRY	$3.1
FRESENIUS KABI	ADALIMUMAB	IDACIO	$0.5
	ADALIMUMAB	IDACIO PSORIASIS	$0.0
	PEGFILGRASTIM	STIMUFEND	$9.1
LILLY	INSULIN GLARGINE	**REZVOGLAR KWIKPEN**	**$0.6**
ORGANON LLC	ADALIMUMAB	**HADLIMA**	**$8.5**
	TRASTUZUMAB	ONTRUZANT	$68.7
	INFLIXIMAB	RENFLEXIS	$295.1
PFIZER	ADALIMUMAB	**ABRILADA**	**$0.0**
	INFLIXIMAB	INFLECTRA	$950.3
	FILGRASTIM	NIVESTYM	$68.3
	PEGFILGRASTIM	NYVEPRIA	$106.3

Biosimilar Sponsor	Proper Name of Molecule	Biosimilar Brand Name (**Bold** = Interchangeable)	IQVIA NSP Sales, CY 2023 (Million 2023 $)
	ERYTHROPOIETIN ALPHA	RETACRIT	$288.7
	RITUXIMAB	RUXIENCE	$668.9
	TRASTUZUMAB	TRAZIMERA	$244.5
	BEVACIZUMAB	ZIRABEV	$607.7
SANDOZ	ADALIMUMAB	ADALIMUMAB ADAZ	$3.1
	RANIBIZUMAB	**CIMERLI**	**$222.7**
	ADALIMUMAB	**HYRIMOZ**	**$2.9**
	ADALIMUMAB	**HYRIMOZ CROHNS**	**$0.4**
	ADALIMUMAB	**HYRIMOZ PED CROHNS**	**$0.0**
	FILGRASTIM	ZARXIO	$185.8
	PEGFILGRASTIM	ZIEXTENZO	$152.9
TEVA PHARM USA	TRASTUZUMAB	HERZUMA	$11.2
	RITUXIMAB	TRUXIMA	$637.0
TOTAL			**$7,695.5**

NSP = national sales perspective
CY = calendar year
n/a = not available/not applicable

Table 8. Biosimilar, Interchangeable, and Reference Product (RP) Sales in CY 2022, Aggregated by Molecule

Molecule and (RP Name)	Products and Launch Dates	2023 IQVIA NSP Sales (Million 2023 $)			
		Biosimilar	Interchangeable	Reference Product (RP)	Total
Adalimumab (Humira)	ABRILADA (12/2023, I) ADALIMUMAB ADAZ (07/2023, I) ADALIMUMAB ADBM (10/2023, I) ADALIMUMAB FKJP (07/2023, B) AMJEVITA (02/2023, B) CYLTEZO (07/2023, I) CYLTEZO CROHNS (08/2023, I) CYLTEZO PSORIASIS (11/2023, I) HADLIMA (07/2023, B) HULIO (09/2023, B) HUMIRA (01/2003, RP) HUMIRA CROHNS (03/2007, RP) HUMIRA PED CROHNS (11/2014, RP) HUMIRA PED ULC COL (03/2021, RP) HUMIRA PSORIASIS (03/2009, RP) HYRIMOZ (07/2023, I) HYRIMOZ CROHNS (07/2023, I) HYRIMOZ PED CROHNS (12/2023, I) IDACIO (08/2023, B) IDACIO PSORIASIS (11/2023, B) YUFLYMA (07/2023, B) YUSIMRY (07/2023, B)	$126.1 (0.4%)	$11.1 (0.0%)	$35,595.9 (99.6%)	$35,733.1 (100.0%)
Bevacizumab (Avastin)	ALYMSYS (10/2022, B) AVASTIN (03/2004, RP) MVASI (07/2019, B) VEGZELMA (04/2023, B) ZIRABEV (01/2020, B)	$1,532.3 (75.1%)	n/a	$506.7 (24.9%)	$2,039.1 (100.0%)
Epoetin Alfa (Procrit)	EPOGEN (06/1989, RP) PROCRIT (02/1991, RP) RETACRIT (09/2018, B)	$288.7 (29.7%)	n/a	$683.9 (70.3%)	$972.6 (100.0%)
Filgrastim (Neupogen)	NEUPOGEN (04/1997, RP) NIVESTYM (10/2018, B) RELEUKO (12/2022, B) ZARXIO (09/2015, B)	$257.2 (72.7%)	n/a	$96.8 (27.3%)	$354.0 (100.0%)
Infliximab (Remicade)	AVSOLA (07/2020, B) INFLECTRA (11/2016, B) INFLIXIMAB (12/2021, RP) REMICADE (09/1998, RP) RENFLEXIS (09/2017, B)	$1,546.6 (45.4%)	n/a	$1,863.5 (54.6%)	$3,410.1 (100.0%)

Molecule and (RP Name)	Products and Launch Dates	2023 IQVIA NSP Sales (Million 2023 $)			
		Biosimilar	Interchangeable	Reference Product (RP)	Total
Insulin Glargine (Lantus)	INSULIN GLARG YFGN (11/2021, I) INSULIN GLARGIN SOLOSTAR (05/2022, RP) INSULIN GLARGINE (05/2022, RP) LANTUS (04/2001, RP) LANTUS (05/2001, RP) LANTUS SOLOSTAR (07/2007, RP) REZVOGLAR KWIKPEN (04/2023, I) SEMGLEE (09/2020, I)	n/a	$580.4 (10.1%)	$5,192.3 (89.9%)	$5,772.7 (100.0%)
Pegfilgrastim (Neulasta)	FULPHILA (07/2018, B) FYLNETRA (05/2023, B) NEULASTA (03/2002, RP) NYVEPRIA (01/2021, B) STIMUFEND (04/2023, B) UDENYCA (01/2019, B) ZIEXTENZO (12/2019, B)	$826.0 (35.8%)	n/a	$1,482.6 (64.2%)	$2,308.7 (100.0%)
Ranibizumab (Lucentis)	BYOOVIZ (07/2022, I) CIMERLI (10/2022, I) LUCENTIS (07/2006, RP)	$36.4 (3.7%)	$239.6 (24.3%)	$709.3 (72.0%)	$985.2 (100.0%)
Rituximab (Rituxan)	RIABNI (01/2021, B) RITUXAN (12/1997, RP) RUXIENCE (02/2020, B) TRUXIMA (11/2019, B)	$1,443.0 (55.5%)	n/a	$1,155.6 (44.5%)	$2,598.7 (100.0%)
Tocilizumab (Actemra)	ACTEMRA (01/2010, RP)	n/a	n/a	$1,686.9 (100.0%)	$1,686.9 (100.0%)
Trastuzumab (Herceptin)	HERCEPTIN (10/1998, RP) HERZUMA (03/2020, B) KANJINTI (07/2019, B) OGIVRI (12/2019, B) ONTRUZANT (06/2020, B) TRAZIMERA (03/2020, B)	$807.9 (71.0%)	n/a	$330.7 (29.0%)	$1,138.6 (100.0%)
TOTAL		$6,864.2	$831.1	$49,304.2	$56,999.7

NSP = national sales perspective
RP = reference product
B = biosimilar
I = interchangeable
n/a = not applicable; no sales in that category for that molecule.

The previous three tables suggest some important inferences:

- The revenue opportunities in the biosimilar marketplace are substantial. In 2023, 86 companies recorded sales of CDER-approved 351(a) biologics. The total invoice

dollar sales in 2023 for 351(a) biologics as reported by IQVIA and based on our identification of CDER biologics, were $269.0 billion. That total was $228.0 billion in 2022 and $201.9 billion in 2021, showing that the market is growing over time.

- Corporate sponsors of biosimilars have been mainly very large international pharmaceutical companies or their subsidiaries and spin-offs, such as Organon (Merck) or Sandoz (Novartis). The reasons for this should become apparent as we investigate the cost and complexity of developing a biosimilar, gaining FDA approval, monitoring the manufacture of the biosimilar, meeting charges of patent infringement by the originator company, and dealing with several other strategic barriers that may arise as the RPC tries to protect its patents and/or market share (discussed below).

2.6 Biosimilar Pipeline

Table 9 summarizes the status of biosimilars in various stages of development up to, but not including, CDER approval, as presented in November 2024 by Cencora (formerly AmerisourceBergen), one of the three largest pharma wholesaler/distributors in the United States [46]. Further details about these biosimilars are included in Table 61 in Appendix B.

Table 9. Summary of Biosimilars in the U.S. Pipeline, by Reference Product (RP) and Development Stage, as of November 1, 2024 [46]

Reference Product (RP) [a] Plain font = no biosimilars yet in market	**RP Approval Date**	**CY 2023 U.S. Invoice Sales of Entire Market (2023 $ millions**	**Preclinical**	**PK/PD Similarity Study**	**Comparative Efficacy Study**	**Pending [b]**	**Total**
ACTEMRA	1/8/2010	$1,686.9			1	1	**2**
AVASTIN	2/26/2004	$2,039.1		1	1	3	**5**
CIMZIA	4/22/2008	$2,251.3		1			1
COSENTYX	1/21/2015	$5,785.4			2		2
ENBREL	11/2/1998	$6,495.6			1		**1**
ENTYVIO	5/20/2014	$4,178.4			2		2
EYLEA	11/18/2011	$9,600.00			3	1	**4**
HERCEPTIN	9/25/1998	$1,138.6			1	2	**3**
HUMALOG	6/14/1996	$5,379.6	2		1	1	4
KEYTRUDA	9/14/2014	$15,676.7			4		4
LANTUS	4/20/2000	$8,904.3	4		1	1	**6**
LUCENTIS	6/30/2006	$988.7			1	1	**2**
NEULASTA	1/31/2002	$2,308.7		1		2	**3**
NEUPOGEN	2/20/1991	$407.0		1		1	**2**
NORDITROPIN	5/8/1995	$2,794.2			1		1
NOVOLOG	6/7/2000	$5,696.9	3		1	3	7
OPDIVO	3/4/2015	$5,480.0			2		2
PERJETA	6/8/2012	$1,635.8			2		2
EPOGEN/ PROCRIT	6/1/1989	$972.6			1		**1**
PROLIA/XGEVA	6/1/2010/ 11/18/2010	$4,627.7			4/6	3	**7/6**
REMICADE	8/24/1998	$3,410.1			1		**1**

Reference Product (RP) [a] Plain font = no biosimilars yet in market	**RP Approval Date**	**CY 2023 U.S. Invoice Sales of Entire Market (2023 $ millions**	**Preclinical**	**PK/PD Similarity Study**	**Comparative Efficacy Study**	**Pending [b]**	**Total**
RITUXAN	11/26/1997	$2,598.7			1	1	**2**
SIMPONI	4/24/2009	$1,746.4			2		2
STELARA	9/25/2009	$16,072.2				3	**3**
TOUJEO	2/25/2015	$8,904.3	1				1
XOLAIR	6/20/2003	$3,076.2			3	1	4
TOTAL	**n/a**	**n/a**	**10**	**4**	**42**	**24**	**80**

Source Biehn & Nelson [47]
n/a = not applicable/not available
CY = calendar year
[a] Bold font indicates at least one biosimilar has already been approved for the RP.
[b] "Pending" means that the biosimilar's precise stage of the approval process could not be determined, and that the candidate biosimilar could be at any stage between BLA submission and final approval.

Several salient aspects emerge from the data presented in Table 9. First, when these pipeline reports were compiled, 12 of the 26 RPs in the table had no FDA-approved biosimilars in their markets; if the biosimilars are approved, they will be the first biosimilar to compete in their markets. These 12 RPs have a total of 58 biosimilar candidates in their pipeline, which is an average of nearly 5 candidates per RP. Second, 14 RPs already have one or more biosimilar competitors approved by FDA to compete in their markets; they have a total of 34 biosimilars in the pipeline, which is an average of 2.4 candidates per RP. Last, denosumab (Prolia/Xgeva), with a total of 13 candidate biosimilars, and Lantus (insulin glargine), with 7 biosimilars seeking FDA approval, represent 25 percent of the 80 pipeline biosimilars.

The U.S. biosimilar pipeline is complex and uneven where certain areas of the pipeline are thriving while others are under-developed. This variation across different markets might be related to several factors. Therapeutic area and disease prevalence are among the key driving factors. High-demand areas such as oncology and autoimmune diseases are more attractive to biosimilar developers because of large patient populations and significant spending. In contrast, biologics treating rare diseases or niche conditions see fewer biosimilar development because the patient population is smaller, limiting potential returns on investment. Patent barriers are another contributing factor to the observed variation. Some biologics have extensive patent protections that can complicate biosimilar development due to the need to design around these patents, which increases development costs. Similarly, pricing and reimbursement policies also play an important role. Those markets where biosimilars face unfavorable reimbursement structures, such as the "buy-and-bill" model under Medicare Part B tend to have slower uptake making them less attractive to invest in. Conversely, biosimilar pipelines for those markets supported by payer incentives or effective formulary placement for biosimilars (such as the CMS Oncology Care Model) are expected to be more robust. Market saturation also plays a role. Crowded markets with multiple competitors are less likely to attract additional biosimilar entry leading to a diminished pipeline.

Additional considerations that may have blunted the drive toward new biosimilar development in the United States according to our SME interviewees, include higher interest rates (which make lower risk investments more attractive and diminish capital available for longer term, higher risk projects such as bringing a biosimilar to market); uncertainty about the effects of recent and apparently imminent legislation that could limit companies' flexibility in setting prices; and uncertainty regarding which regulatory options FDA will implement regarding issues such as the requirement for CES. It is also quite possible that the inhibitory effects of the COVID-19 pandemic on drug development are still being reflected in these data.

3 STUDY OBJECTIVES

Using public and proprietary data sources coupled with information elicited from subject matter experts (SMEs) via semi-structured interviews, we examine the biosimilar development process as well as the factors that influence the cost, probability of success, and time spent at each development stage. We then develop a valuation model to estimate the ENPV of bringing a biosimilar to the U.S. market. The model accounts for failure and capital costs; variations in market size; number of potential competitors; and product complexity among other factors. Using the model, we then examine the impact of select barriers and incentives designed to eliminate or mitigate those barriers.

4 DATA AND METHODS

4.1 Analytical Framework for Estimating Biosimilar Development and Approval Costs

4.1.1 Steps of Biosimilar Development

Developing a biosimilar candidate involves a series of complex steps that are likely to be much more time consuming and costly than the backward engineering of a small molecule brand drug, which is the first step in producing a generic version. Approval by CDER is not a foregone conclusion, but the agency does urge biosimilar sponsors to consult with them early and often to ensure that sponsors understand the standards their application must meet. The manufacturing and monitoring methods must be designed to avoid and detect, respectively, variabilities greater than those measured for the RP's quality attributes.

Having decided to pursue CDER approval for a biosimilar of, for instance, a specific mAb reference drug, a biosimilar company will normally follow the steps below [48]:

- Obtain numerous (sometimes as many as 100 or more) batches of the RP.
- Thoroughly characterize (i.e., measure) as many of the CQAs of the RP as possible. This is described as "an extensive exercise."
- Establish the range of variation for each CQA of the RP.
- Analytical characterization, typically including assessment of physicochemical attributes (such as primary and higher-order structure, purity, and glycosylation) and functional attributes (which help evaluate the molecule's mechanism of action and intended biological effect).

- Biological assays enable determination of the potential impact of observed structural differences between the biosimilar and RP on the efficacy or safety of the product.
- With the current status of science, *in vitro* tests are particularly sensitive to detect differences between closely related molecules.
- All of the characterized attributes and their corresponding ranges comprise the "fingerprint" of the originator product. The fingerprint provides the standards against which the biosimilar will be measured.
- Matching this fingerprint is the goal of biosimilar development, and it usually happens one quality attribute at a time, ensuring that the biosimilar is reverse engineered to similar ranges.

Once the RP's CQAs and their ranges of variability have been established, the biosimilar sponsor then must:

- Engineer a new process to ensure that the biosimilar matches the originator fingerprint as closely as possible.
- Screen hundreds of new cell lines until the fingerprint of the biosimilar falls within the variability ranges established for the RP, one quality attribute at a time.
- Adjust the cell culture and purification process conditions continuously in order to confirm and maintain the similarity of the biosimilar and RP molecules.

Notably, analytical similarity is established and manufacturing begins early in the process, and matching the biosimilar to the originator's fingerprint is an ongoing effort. "This front-loading of analytical characterization and process development ensures that there should be little residual uncertainty, in that the molecules will have similar clinical efficacy and safety because the molecules have been demonstrated to be highly similar at the molecular level, using the most sensitive analytical methods available" [48]. A recent study of 246 biosimilar projects in the United States, Europe, and Japan estimated the probability of successful emergence of a biosimilar candidate from the preclinical stage at 53 percent [22].

Manufacturing and quality control of biosimilars is inherently complex and painstaking. FDA scrutinizes manufacturing plans and plants scrupulously and any change in manufacturing of any biosimilar prior to FDA approval requires a comparability study to ensure that the biosimilar's CQAs remain on target with the RP. "Although all [manufacturing] changes are evaluated on a case-by-case basis, **several assessments – including of batch analyses, in-process control validation, characterization and stability testing – must be conducted to confirm that process changes do not influence critical quality attributes (CQAs)**, and are therefore not expected to have an adverse impact on safety or efficacy [18,20]" [49] [emphasis added].

Although potential variabilities after a manufacturing change can usually be resolved by comparability studies, there have been occasions when this is not the case. "For example, the scale-up of production of Myozyme/Lumizyme (alglucosidase alfa) showed substantial

differences between the pre- and post-change product; as such, a new license application was required that included clinical assessment" [48].

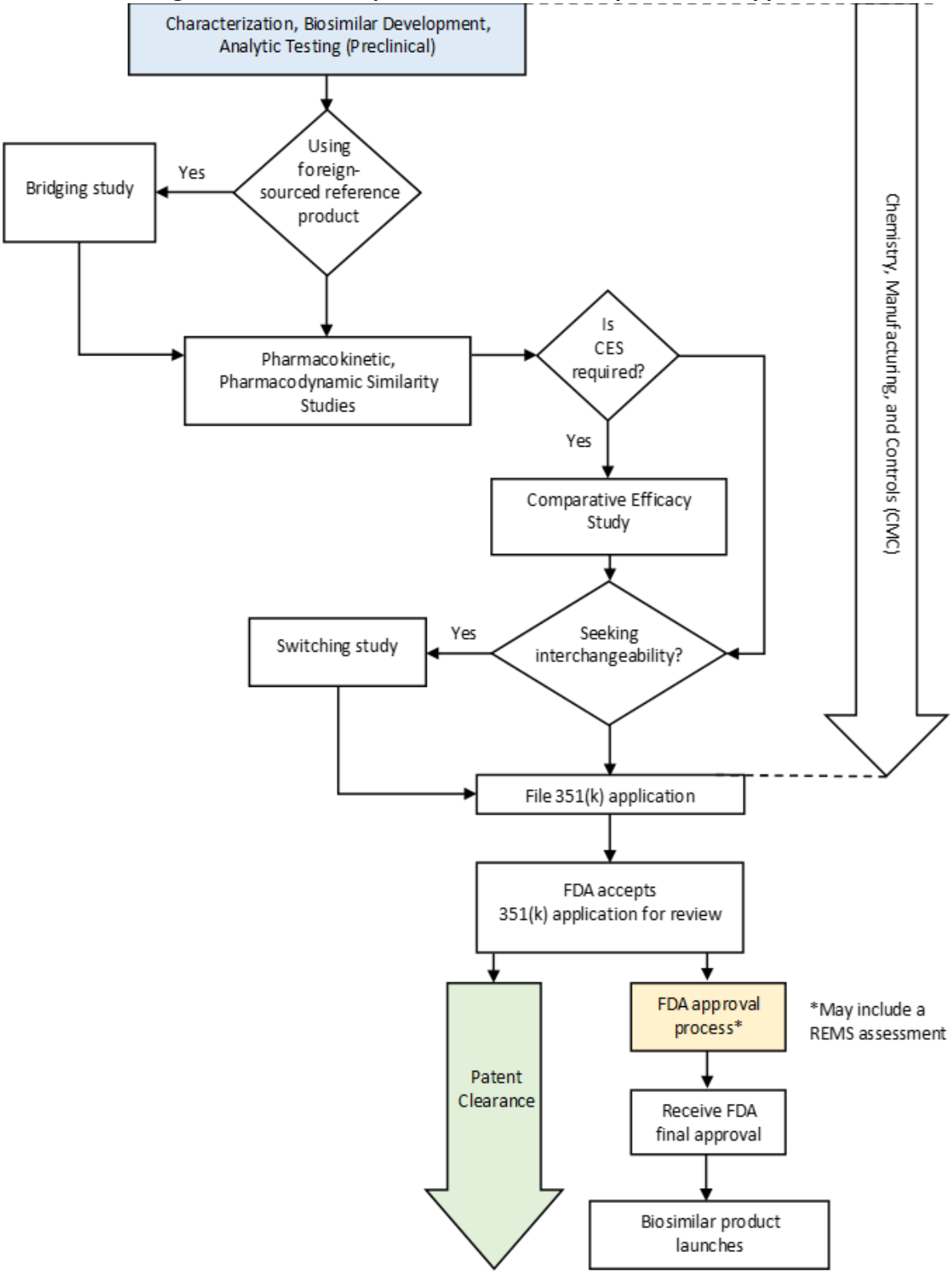
In Figure 1 we present the analytical framework for examining biosimilar development and approval costs as well as market entry/exit decisions. The framework described below lays out the stages of biosimilar development and approval including (1) characterizing a biologic RP; (2) development of the candidate biosimilar; (3) *in vitro* comparative bioassays; (4) accelerated and real-time shelf-life testing; (5) design and implementation of the production-scale manufacturing process; (6) obtaining suitable quantities of RP for use in clinical studies; (7) application for investigational new drug (IND) license and payment of initial biosimilar product development (BPD) fee; (8) a bridging study if an RP from a foreign source is being used; (9) establishing pharmacodynamic (PD) and PK profiles through clinical testing; (10) eliminating residual uncertainties establishing safety and efficacy through comparative efficacy studies; (11) preparing and submitting a 351(k) application to CDER; and (12) responding to any CDER requisites for ultimate approval if CDER does not approve the 351(k) application as submitted. We also consider costs associated with patent litigation and commercialization of the approved product.

The framework described below forms the basis for the operational model that will enable a user to create different scenarios by altering model parameters, such as the RP, clinical study characteristics (e.g., type of subject, location of study), market size, entry order of the biosimilar product (i.e., first through fifth), level of biosimilar adoption (typical or high), and then calculating ENPV of the biosimilar development project.

Figure 1 lays out the main steps associated with bringing a new biosimilar to market based on information gathered from the published literature, FDA guidance documents, white papers, public presentations, and a series of interviews with SMEs from industry, academia, and the public sector. Figure 2 and Figure 3 provide more detail on the initial stage of characterization, biosimilar development, and analytic testing; FDA approval process; and the patent clearance steps. While we estimated some costs at aggregate levels (e.g., for multiple boxes), these diagrams show the components that contribute to those cost estimates. (For a discussion of the estimated values and data sources, see Section 4.1.2.)

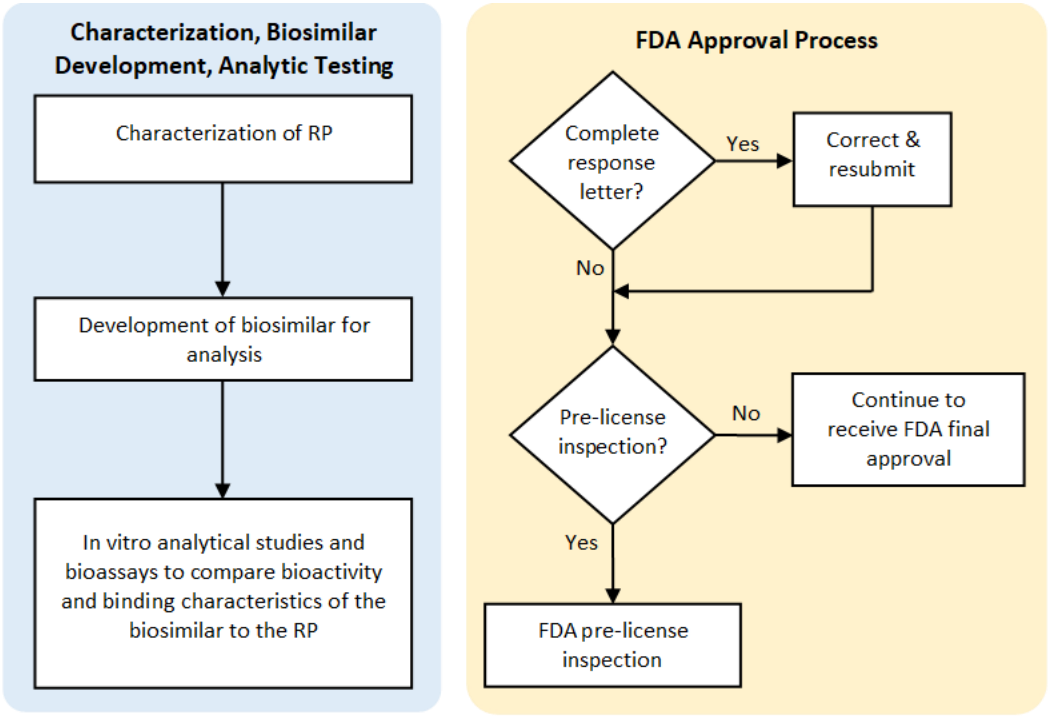
Each development stage depicted in the figure involves a range of activities that span several months and has an associated cost. The ability of the biosimilar developer to proceed to the subsequent development stage requires successful completion of the prior development stage, which is associated with a transition success probability. In this framework, which is similar to that of DiMasi, et al. [50] for new drugs, if the biosimilar fails to emerge successfully from a given stage, then the company will abandon the development effort. The transition success probabilities are calculated on a per-product basis and generally account for the fact that multiple attempts may be required for a biosimilar development project to succeed at a given stage.

Figure 1. Process Map for Biosimilar Development and Approval



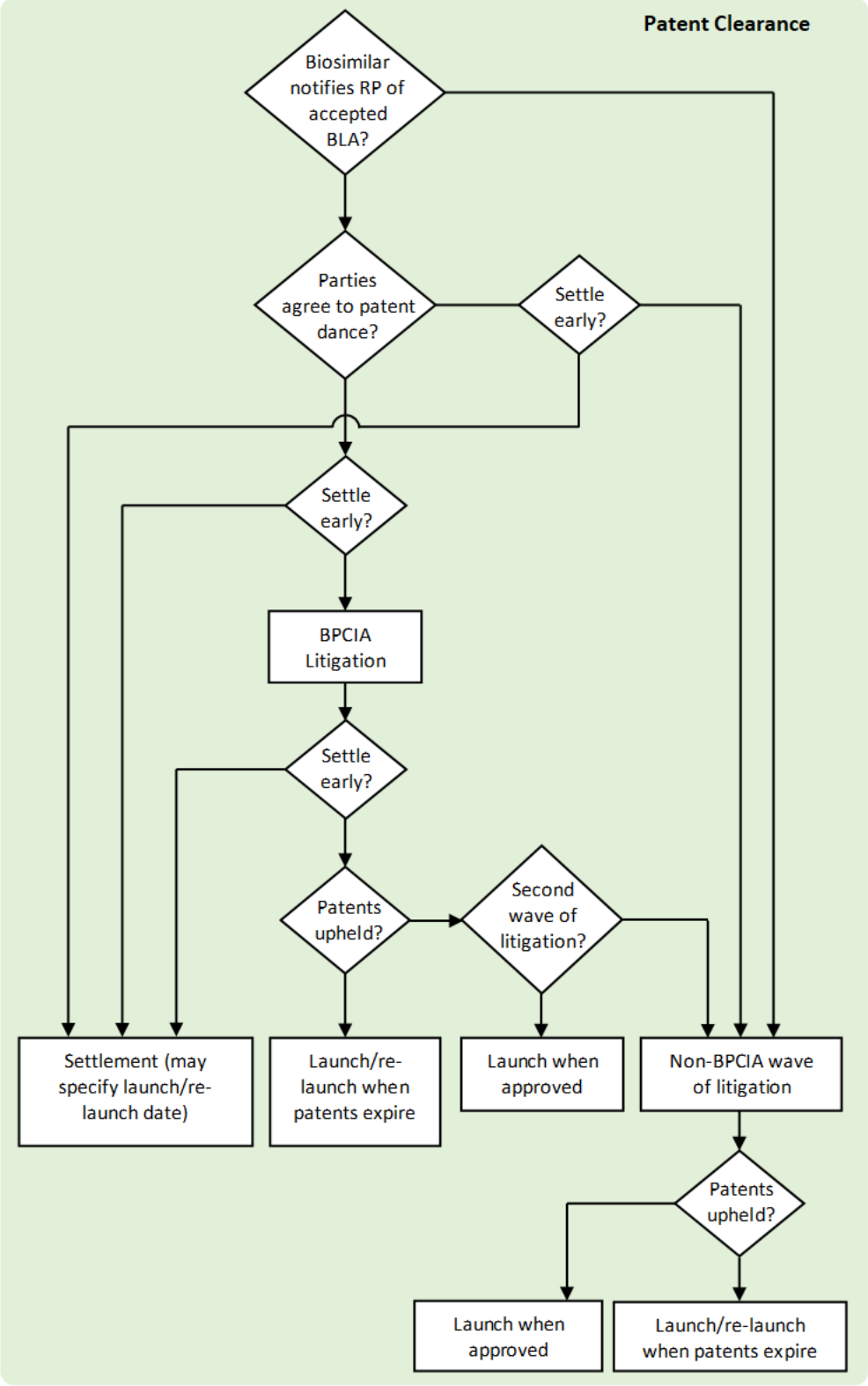
Note: Colors identify processes that are shown in greater detail below (see Figure 2 and Figure 3).

Figure 2. Sub-Process Map for CMC and FDA Approval Process



Note: For additional detail on the left sub-process (Characterization, Biosimilar Development, Analytic Testing), see Table 12.
CMC = chemistry, manufacturing, & controls
RP = reference product

Figure 3. Sub-Process Map for Patent Clearance



Notes: Re-launching would occur if the biosimilar product launched at risk before clearing the RP's patents.
BLA = Biologics License Application; BPCIA = Biologics Price Competition & Innovation Act; RP = reference product

4.1.2 Calculating Expected Capitalized Costs

The total cost and duration of a given biosimilar development project depend on the pathway the developer follows in the depicted process diagram, which is largely driven by strategic business considerations, such as pursuing interchangeability status to gain a competitive advantage, opting for the patent dance, among others. Most of our analyses, however, use a baseline development scenario described in detail below and informed by expert interviews [51].

We can estimate the total cost to develop a biosimilar drug by considering the relevant stages of development and their associated costs, durations, opportunity cost of capital, and transition success probabilities. If the cash outlay (also known as out-of-pocket cost) associated with a given development stage *j* is C_j then the expected cost per approved biosimilar product, $E(C_j)$, is higher because it incorporates the cost of failures. Using the methods of DiMasi et al. [52], the expected cost per approved biosimilar product, $E(C_j)$, is computed by dividing this cost by the probability of successfully transitioning from stage *j* to launch, P_j, i.e.,

$$E(C_j) = \frac{C_j}{P_j} \tag{1}$$

where P_j is the product of the remaining development stage transition success probabilities, p_j:

$$P_j = \prod_j p_j \tag{2}$$

Assuming that cost for a given development stage is distributed uniformly over the length of that stage, t_j, the capitalized cost, CC_j, that accounts for the opportunity cost of the investment in the biosimilar is then given by the following formula, as discussed in DiMasi et al. [53]:

$$CC_j = \int_{t_{j,e}}^{t_{j,b}} \left(\frac{C_j}{t_j}\right)(e^{rt})dt \tag{3}$$

where *r* is the cost of capital that captures the time value effect; $t_{j,b}$ is the time from the beginning, *b*, of the given development stage to biosimilar launch, and $t_{j,e}$ is the time from the end, *e*, of the given stage to biosimilar launch. The above equation then becomes:

$$CC_j = \frac{\left(C_j \big/ t_j\right)}{r}(e^{rt_{j,b}} - e^{rt_{j,e}}) \tag{4}$$

Given the above equations, we can compute the expected capitalized cost of development stage *j* that accounts for the cost of failures as well as the cost of capital as:

$$E(CC_j) = \frac{CC_j}{P_j} \tag{5}$$

Then, the total expected capitalized cost, $E(CC_j)$, of developing a given biosimilar is the sum of the expected capitalized cost of each applicable development stage *j* and is given by:

$$E(CC_i) = \sum_j E(CC_{ij}) \quad (6)$$

4.1.3 Cost Model Parameters and Assumptions

Table 10 provides the model parameters to estimate to operationalize a biosimilar cost model. To the extent that reasonable ranges can be defined for these parameters, it will enable the model user to examine the likely range for expected total cost of development and commercialization by product characteristics (i.e., therapeutic area, molecule complexity), development pathway, and development characteristics (i.e., location of studies, type of studies, whether a device is developed alongside the drug).

Table 10. Model Parameters to be Estimated

Model Parameter	Variable
Real opportunity cost of capital	r
Out-of-pocket cost (in $ 2022)	$C_j^{(k)}$
Duration (in months)	$t_j^{(k)}$
Duration from start of stage *j* to start of stage *j* + 1 (in months)	$\left[t_j^{(b)} - t_{(j+1)}^{(b)}\right]^{(k)}$
Transition success probability	$p_j^{(k)}$

Notes: *j* represents the stage of development, with *j* = 1, …, *N* and with *N* representing the final stage of development. *k* represents a particular group of drugs, e.g., drugs with a particular therapeutic area or drugs with a particular molecular complexity. The impact of these drug characteristics on our estimates is discussed in depth below.

The following sections discuss the model parameters estimated and provide more detail on the stages of biosimilar development and approval. As discussed in detail in the following sections, the model parameter estimates are based on published studies; data extracted from clinicaltrials.gov on biosimilar studies; and interviews with a small convenience sample (n=26) comprised of biosimilar developers, original biologic company representatives, IP attorneys, pharmacy benefit managers, prescribing physicians, and clinical pharmacy managers, involved in one or more aspects of the complex series of economic, scientific, technological, legal, and marketing processes that bringing a biosimilar product to market entails. Our interviews were semi-structured in nature and elicited estimates of the costs to the biosimilar sponsor of the various steps in product development; costs of generating the bioanalytic and clinical study data necessary for a successful biosimilar license application via the 351(k) approval pathway, as well as costs of any patent litigation resulting from the biosimilar's attempt to enter the market. In addition, we also elicited estimates of the impacts of potential barriers to market entry and estimates of the value of incentives currently available and potential incentives proposed as elements of policy alternatives. Since a statistical survey was infeasible, the opinions elicited may not be fully representative of the population of interest and have high variability. Nonetheless, given the dearth of data on biosimilar development costs, they represent the best available information for modeling purposes.

4.1.3.1 Real Opportunity Cost of Capital

The real opportunity cost of capital, *r*, represents the rate of return (net of inflation) that the biosimilar company would otherwise be able to earn at the same risk level as the

investment in the new biosimilar selected. The value of *r* is expected to vary by company-specific factors, such as existing product portfolio and size of company, as well as other exogenous factors, such as economic and regulatory climate for biosimilar development. Additionally, manufacturers' classification as either a pharmaceutical company or a biotechnology company, both of which might develop a biosimilar, influences the value of *r*. Table 11 presents estimates of real opportunity cost of capital from different sources. From the table, the value of *r* ranges from 8 percent to around 13 percent. As the baseline value in our analysis, we used 8.20 percent, which is the average for the U.S. biotechnology and U.S. pharmaceutical industries in 2023 based on Damodaran [54].

Table 11. Real Opportunity Cost of Capital Estimates

Data Source	Firm Size	Type of Model	Study Period	Classification	Real Opportunity Cost of Capital
DiMasi, et al. [50]	All	CAPM	2010	All	9.4%
Damodaran [54]	All	CAPM	2023	Biotech	8.3%
Damodaran [54]	All	CAPM	2023	Pharma	8.0%
Harrington [55]	All	CAPM	2006–2008	Biotech	11.8%
	Large	CAPM	2006–2008	Biotech	10.2%
	Small	CAPM	2006–2008	Biotech	13.2%
Harrington [55]	All	CAPM	2006–2008	Pharma	9.3%
	Large	CAPM	2006–2008	Pharma	9.5%
	Small	CAPM	2006–2008	Pharma	8.6%

CAPM = capital asset pricing model

4.1.3.2 Pre-clinical Research and Development

The initial steps in the development of a biosimilar are much more complex than those involved in developing a generic chemical drug candidate. Although we present them sequentially (Table 12), some of the steps or procedures may overlap or be conducted concurrently.

In brief, during the preclinical research and development stage (Table 12), the biosimilar developer characterizes the mechanism of action and CQAs of the RP molecule; selects the cell line and production process to manufacture quantities of the biosimilar adequate for in vitro testing; establishes the product's in vitro biosimilarity to its RP through a series of tests and assays; and establishes the product formulation's stability through real time and accelerated stability testing. SMEs indicated that preclinical biosimilar development costs and durations would vary based on the complexity of the molecule. When a molecule is highly complex, such as many receptor-fusion proteins, more testing may be required during preclinical development, thereby driving up costs and timelines (CDMO 1) [51]. In addition, preclinical development must often circumvent existing patents, which can reportedly increase the difficulty of development (CMC 1). Further, acquisition cost of RP sufficient for both analytical and clinical study could be significant. Some RPs are expensive and difficult to procure, potentially driving up costs. Thus, alongside the structure and size of the molecule itself, the quantity of patents held by the RP may also increase complexity and thereby increase preclinical costs and timelines.

We present the average cost, duration, and phase transition success probability estimates disaggregated by molecule complexity associated with this stage in Table 13.

Table 12. Early Development Stages of a Biosimilar

Preclinical Development Stage	Description
Characterization of RP	Obtain the required, usually small, quantity of the RP for analysis.
	Determine structure and variation of RP via liquid chromatography/mass spectrometry to determine its: Molecular weight of intact and reduced protein Amino acid sequence, peptide map [56]. Co- and post-translational modifications (i.e., amino acid side chain modification in some proteins after their biosynthesis. Up to 400 types, including phosphorylation, glycosylation, ubiquitination, and S-nitrosylation. Disulfide linkage locations (bond mapping critical to protein folding, structural stability) [57]. Glycan profile ("most challenging" per CMC company interview). Higher-order structure (using hydrogen-deuterium exchange mass spectrometry—HDX-MS, often in combination with cryo-electron microscopy).
Development of biosimilar for analysis	Host cell line selection and gene insertion. *Potential issues:* Gene mutation; inconsistent protein expression among host cells; impurities in host cells.
	Cell culture volume expansion in bioreactor to production levels under targeted conditions (temperature, media, pH, etc.). *Potential issues:* Inadequate productivity, product degradation, post-translational modifications, host cell impurities
	Centrifugation/Depth Filtration: Removal of host cells and impurities
	Chromatographic purification
	Virus Filtration. *Potential issues:* Remaining impurities; protein degradation/aggregation; biological activity
	Formulation. Final concentration of protein, placement in buffer and long-term containers. *Potential issues:* Protein aggregation; impurities, shelf-life problems
In vitro analytical studies and bioassays to compare bioactivity and binding characteristics of the biosimilar to the RP	Obtain adequate amounts of RP for in vitro studies (and subsequent PK/PD similarity and clinical efficacy studies)
	Tests may include enzyme-linked immunosorbent assay, flow cytometry, surface plasmon resonance, sensorgram comparison, and parallel line analysis
	Perform shelf-life studies, real-time and/or accelerated
	Submit IND application for the biosimilar (including information for the reference product, if using an unapproved comparator product, i.e., a foreign-sourced version of the reference product that has not been approved by FDA)
	If using unapproved comparator in lieu of approved RP, perform in vitro bridging study to demonstrate comparability of RP and unapproved comparator
	Design and implement manufacturing process and quality monitoring program

RP = reference product
CMC = chemistry, manufacturing, & controls
IND = investigational new drug

Table 13. Estimated Baseline Model Parameters for the Preclinical Research and Development Stage

Baseline Model Parameter	Low Complexity [a]	Medium Complexity [a]	High Complexity [a]	Source
Obtaining RP for Preclinical Development	$1.0 million	$1.0 million	$1.0 million	CMC Company 1. Includes Preclinical and CMC RP Needs.
Characterization of RP	$2.0 million	$3.2 million	$4.4 million	CMC Company 1, CDMO 1
Development of Biosimilar for Analysis	$2.0 million	$3.2 million	$4.4 million	CMC Company 1, CDMO 1
In Vitro Analytical Studies and Bioassays	$2.0 million	$3.2 million	$4.4 million	CMC Company 1, CDMO 1
Total Preclinical Development Out-of-Pocket Cost (in 2023 $)	$7.0 million	$10.6 million	$14.2 million	CMC Company 1, CDMO 1
Total Preclinical Phase Duration	23 months	32 months	41 months	CMC Company 1, CDMO 1
Transition Success Probability	75%	63%	50%	CMC Company 1

RP = reference product
CMC = chemistry, manufacturing, & controls
[a] When source provided a range of values, the midpoint of the range was used for the average calculation. The upper and lower points of the range, which are not presented here, were used for high and low estimates, respectively.

4.1.3.3 PK/PD Similarity and Comparative Efficacy Studies

Upon successful completion of the preclinical research and development stage, the focus then turns to testing the candidate biosimilar in human subjects to further ensure that its PK, PD, and immunogenic profile is consistent with those of the RP.

Prior to beginning PK/PD similarity studies, the sponsor must submit an IND application to obtain permission from the FDA to start human clinical studies and to ship an experimental drug across state lines if the sponsor is planning to conduct these studies in the United States.

PK/PD similarity studies are conducted to establish that PK and PD (if available) profiles and immunogenicity of the biosimilar are similar to that of the RP. These studies are typically smaller and less costly than CES. Major drivers of cost for PK/PD similarity studies include whether the study subjects are healthy volunteers or patients. The use of healthy volunteers results in lower costs and is overwhelmingly preferred for PK/PD similarity studies by biosimilar sponsors (Table 14). The sample size and number of studies needed are also major drivers of total PK/PD similarity costs. Similarly, the need for a three-arm bridging study, which may either increase sample size compared to a typical two-arm PK/PD similarity study or necessitate an additional PK/PD similarity study, is a cost driver. However, conducting a bridging study may reduce the costs of subsequent clinical studies owing to the lower cost of non-US RPs. The need for device development or usability studies, such as for those biosimilars which might be administered via a manufacturer-developed auto-injector (e.g., Cyltezo) is another cost driver

and typically results in a longer duration for the PK/PD similarity stage. Finally, the location of each of these studies may affect costs.

In addition to the above cost drivers related to the PK/PD similarity study characteristics, PK/PD similarity study costs further vary by therapeutic area, with oncology and hematology studies typically having the highest costs.

CESs are conducted to buttress evidence of CES established by in vitro and PK/PD similarity studies. As with PK/PD similarity studies, sample size and duration impact CES costs. Average CES requires several hundred patients and several years to complete, thus driving up costs as compared to PK/PD similarity studies. Similar to PK/PD similarity studies, CES costs vary by therapeutic area, with oncology and hematology studies being significantly more expensive than those in either the immunology or "other" group.[22]

To estimate the average number of subjects and duration of biosimilar clinical studies, we compiled data from the Drugs@FDA database, clinicaltrials.gov, and EMA assessment reports. For each biosimilar approved for the U.S. market, we examined the review documents posted to the Drugs@FDA database and identified available study characteristics, such as sample size and study arms. Submitted studies were included regardless of whether they served as a pivotal study for the BLA review or other purposes, such as demonstrating cost effectiveness. Studies were also included regardless of whether the comparator was the RP, provided that they met the criteria for being listed in FDA documentation (e.g., studies comparing different modes of delivery for the biosimilar). Exclusion criteria included studies not listed in FDA documentation, such as post-marketing studies; studies which were phase IV; studies which did not have a unique study ID (e.g., extension studies with the same ID as the parent study); and studies which utilized a comparator group for which there was no bridge submitted.

We used clinicaltrials.gov data to supplement sample size information where such data were not clearly indicated in the review documentation and to obtain data on the duration of each study. Finally, EMA assessment reports were used to supplement sample size data where this information was not available from FDA review documentation or clinicaltrials.gov.

Overall, data were collected for 43 biosimilars, corresponding to 14 RPs. Table 14 summarizes these data. When calculating average PK/PD similarity sample size and duration using the compiled data, we first calculated the total sample size and end-to-end duration across all included PK/PD similarity studies for a given drug. We then divided the 43 biosimilars for which we had data into distinct groups based on (1) therapeutic area, (2) inclusion of a bridging study, and (3) inclusion of a device development study. Where data were available, we calculated the overall averages for PK/PD similarity sample size and duration within each distinct group. Where data were unavailable, we relied on assumptions and relationships within the available data to estimate group averages (see Table 15). In addition to sample size and

[22] "Other" is defined as the average amongst all therapeutic areas excluding oncology, hematology, and immunology.

duration for PK/PD similarity, we calculated the average overlap between the end of PK/PD similarity studies and the beginning of CES.

A similar approach was utilized for calculating CES sample size and duration. However, data were exclusively divided by therapeutic area. For CES switching studies, a different approach was used due to the paucity of data. For each of the five drugs in our database that included a switching study (all of which were immunology drugs), we calculated the ratio of the switching study estimate to the average CES estimate for the same drug. We then averaged the five ratios and applied the average ratio to all drug categories to estimate the sample size and duration of a switching study for the given category. We further calculated the average overlap between switching studies and CES in our database and assumed this overlap applies to all therapeutic areas. No switching study overlapped with PK/PD similarity stage in our data. Table 16 presents the results of these analyses.

Table 14. Characteristics of Biosimilar Clinical Studies, 2012–2022

Type of Study	Number of Unique RPs	Number of Unique Biosimilars	Number of Clinical Studies	Studies with Healthy Subjects	Studies with Patients
PK/PD similarity, Bridging [a]	9	29	34	32	2
PK/PD similarity, Overall	12	40	97	87	10
CES	13	36	54	0	54
Total	14	43	151	87	64

RP = reference product

Note: Where a number is listed, it represents the number of studies included to obtain the result in that cell. The number is lower for duration per study because duration data were not readily available for all studies in the sources consulted.

[a] Bridging studies were defined in the database as any study with three arms consisting of the biosimilar, the RP approved by FDA, and a version of the RP approved by regulators in another jurisdiction (but not by FDA). Sources: Drugs@FDA, ClinicalTrials.gov, EMA assessment reports.

Table 15. PK/PD Similarity Study Characteristics by Group [a]

Therapeutic Group	Study Characteristic	Bridge + Device	Bridge Only	Device Only	No Bridge, No Device
Hematology [b]	Average Sample sizes	583	267	617	283
	Duration (Mos)	39	12	31	10
	Overlap (Mo)	16	8	7	2
Immunology	Sample Size	583	267	617	283
	Duration (Mo)	39	12	31	10
	Overlap (Mo)	16	8	7	2
Oncology [c]	Sample Size	n/a	316	n/a	334
	Duration (Mo)	n/a	30	n/a	24
	Overlap (Mo)	n/a	7	n/a	3
Other [b]	Sample Size	583	267	617	283
	Duration (Mo)	39	12	31	10
	Overlap (Mo)	16	8	7	2

n/a = not applicable

[a] All averages were calculated both including and excluding drugs with incomplete data (e.g., a drug with duration data for only 2 of 3 studies). In general, we would expect missing data to bias the estimates downwards, but due to

the limited overall sample size and variation between drugs, we found that this was not consistent within our data. Thus, for sample size and duration estimates, we used the larger of the two estimates. For estimates of the overlap between the PK/PD similarity and CES studies, we used the smaller of the two estimates. In both cases, we selected the more conservative estimate that will result in higher overall development costs.
[b] Data for these groups is not available because no existing biosimilars fall within these therapeutic areas. Therefore, we assumed their sample sizes and durations were equivalent to those for the immunology group. The oncology group was not selected because SMEs indicated that oncology study durations may be notably different than those for other therapeutic areas.
[c] Oncology drugs are assumed to not involve device development. Therefore, no estimates are provided for these groups.

Table 16. CES Averages, By Group [a]

Therapeutic Area [b]	Parameter	CES	CES Switching Study [c]
Hematology	Sample Size	697	320
	Duration (Mo)	28.5	15.7
	Overlap (Mo)	n/a	4.6
Immunology	Sample Size	697	320
	Duration (Mo)	28.5	15.7
	Overlap (Mo)	n/a	4.6
Oncology	Sample Size	632	293
	Duration (Mo)	40.9	24.9
	Overlap (Mo)	n/a	4.6
Other	Sample Size	697	320
	Duration (Mo)	28.5	15.7
	Overlap (Mo)	n/a	4.6

n/a = not applicable
[a] All averages were calculated both including and excluding drugs with incomplete data (e.g., a drug with duration data for only 2 of 3 studies). In general, we would expect missing data to bias the estimates downwards, but due to the limited overall sample size and variation between drugs, we found that this was not consistent within our data. Thus, for sample size and duration estimates, we used the larger of the two estimates. For estimates of the overlap between the PK/PD similarity studies and CESs, we used the smaller of the two estimates. In both cases, we selected the more conservative estimate that will result in higher overall development costs.
[b] Data are not available for hematology and "other" because there are no existing biosimilars falling within these therapeutic areas. Therefore, we assumed their sample sizes and durations were equivalent to those for the immunology group. The oncology group was not selected because SMEs indicated that oncology study durations may be notably different than those for other therapeutic areas.
[c] Switching study estimates for sample size and duration are based on ratios developed from the available five drugs with switching studies in our database. The formula for estimating these values is: (Average Ratio amongst all drugs with switching studies) * (Average estimate for the given group / Average # of studies for the given group). Estimates for the overlap between CES studies and switching studies are based on the average overlap in our database.

In vivo biosimilarity studies can be based on PK, PD, immunogenicity, or clinical endpoints. PK endpoint-based studies are often performed on healthy volunteers. FDA says: "Clinical PK and PD studies should be conducted in healthy subjects if the product can be safely administered to them" (U.S. Food and Drug Administration, 2016). However, "with biosimilars it may be preferable to draw subjects from the patient demographic most likely to provide a sensitive measure of differences between the biosimilar and reference product" [58]. Yet, within the sample of 97 PK/PD similarity biosimilar studies we examined (Table 14), all but ten studies submitted by the biosimilar applicants used healthy subjects. The average sample size and duration for PK/PD similarity studies varied by group, ranging from 267 to 617 subjects and

from 10 to 39 months (Table 15). Bridging studies were conducted for roughly two-thirds of biosimilars, which suggests that the cost of obtaining sufficient amounts of the U.S. RP for use as a study comparator may be greater than the cost of conducting a bridging study necessitated by the use of non-U.S. licensed comparator sourced from European or Asian markets.

Compared to PK/PD similarity studies, the average sample size for CES was similar, ranging from 293 to 697 depending on therapeutic area (Table 16). This similarity is likely due to a higher quantity of studies being conducted in PK/PD similarity phase as opposed to CES. For example, amongst our sample, the average number of studies conducted in PK/PD similarity phase was 2.5 compared to 1.5 for CES. Therefore, the average sample size per study is lower in PK/PD similarity phase than in CES, as expected. Sample sizes amongst individual CESs in our data ranged from 15 to 875.[23]

PK/PD Similarity Studies on Healthy Volunteers

PK/PD similarity studies on healthy volunteers involve PK endpoints and compare the systemic effects and bioavailability of the candidate biosimilar with the RP by comparing specific relevant physical parameters. Frequently, these include comparing the following parameters:

- Maximum observed concentration (C_{max}) of biosimilar and RP after single dose.
- Time to C_{max} of biosimilar and RP after single dose.
- For biosimilar and RP, compare areas under their concentration-time curves from before first dose to last measurable concentration.
- Total area under the curve (AUC) after extrapolation from time *t* to time infinity of biosimilar and RP following a single dose.
- Elimination rate constant of biosimilar with RP following a single dose.
- Apparent terminal elimination half-life of biosimilar with RP following a single dose.
- Volume of distribution of biosimilar with RP following a single dose.
- Apparent clearance of biosimilar with RP following a single dose.

The number of healthy volunteers used in bioequivalence studies of generic chemical drugs varies considerably, but in the analysis by Davit et al. [59], the upper end of the range was 134 subjects, and the average was 55 for the most variable drugs. Among the PK/PD similarity studies that we examined, the number of healthy volunteers ranged from 10 to 577 with an average of about 155 healthy volunteers per study.[24]

The cost per subject for PK/PD similarity studies were obtained from Sertkaya et al. [30, 60]. Cost per subject were available disaggregated by region and therapeutic area. For this model, we have adopted the cost per subject values for the U.S., EU, and Asia regions.

[23] The study listed as having 15 subjects was apparently conducted for local product licensing and was ongoing at the time of submission.

[24] When including PK/PD similarity trials with patients, the average sample size per trial decreases to about 150 subjects per trial.

Additionally, we have adopted the cost per subject values for hematology, immunology, and oncology. For the "other" therapeutic area categorization, we calculated the average cost per subject from all therapeutic areas excluding the above-mentioned three.

In addition, we assumed that the cost per subject for PK/PD similarity phase will vary based on whether the studies use healthy subjects, patients, or both. We assume that the PK/PD similarity phase cost per subject data represents healthy subjects and that cost per patient is 50 percent higher than the cost per healthy subject. We further assume that when a PK/PD similarity program includes both healthy subjects and patients, the breakdown is 58 percent and 42 percent, respectively. These figures were estimated based on the average proportions among drugs in our database that included both healthy subjects and patients in their PK/PD similarity studies.

Table 17 below presents an example of the baseline estimates calculated for PK/PD similarity studies, for the assumed scenario of a PK/PD similarity study that only uses healthy subjects in the United States. Whereas our estimated costs vary by location and subject type, phase duration and transition success probability do not.

Table 17. Estimated Baseline Model Parameters for PK/PD Similarity Studies, By Therapeutic Area

	Bridge + Device	Bridge, No Device	No Bridge, Device	No Bridge, No Device
Hematology				
Out-of-Pocket Cost (in 2023 $) [a]	$203.7 million	$93.3 million	$215.6 million	$99.0 million
Phase Duration (Mo)	39	12	31	10
Transition Success Probability [b]	80%	80%	80%	80%
Immunology				
Out-of-Pocket Cost (in 2023 $) [a]	$37.0 million	$16.9 million	$39.2 million	$18.0 million
Phase Duration (Mo) [c]	39	12	31	10
Transition Success Probability [b]	80%	80%	80%	80%
Oncology				
Out-of-Pocket Cost (in 2023 $) [a]	n/a	$32.7 million	n/a	$34.5 million
Phase Duration (Mo) [c]	n/a	30	n/a	24
Transition Success Probability [b]	n/a	80%	n/a	80%
Other				
Out-of-Pocket Cost (in 2023 $) [a]	$34.6 million	$15.9 million	$36.7 million	$16.8 million
Phase Duration (Mo) [c]	39	12	31	10
Transition Success Probability [b]	80%	80%	80%	80%

n/a = not applicable/not available

a] Out-of-pocket costs shown here reflect those estimated for a PK/PD similarity program made up of exclusively healthy subjects located in the United States. These values are calculated as the average sample size (Table 15) multiplied by the cost per subject (obtained from Sertkaya et al. [30, 60]).

[b] Transition success probability was obtained from a report published by the Biotechnology Innovation Organization [61]. Biosimilar success rates were not disaggregated by therapeutic area or study characteristics and thus, we assume that an 80 percent success rate applies to all therapeutic areas.
[c] Phase duration estimates represent the average of SME reported values.

Comparative Efficacy Studies (CESs) on Patients

CESs are conducted on patients primarily to compare the therapeutic effects of the biosimilar formulation and the RP, and to ensure that the biosimilar is comparably safe and efficacious as the RP. Historically, they were often needed if the drug in question has a localized effect (e.g., diminishing psoriatic plaque, shrinking a tumor). However, not all biosimilars will require a CES for approval and FDA is encouraging applicants to generate adequate in vitro and PK/PD similarity data to obviate the need for a CES. Where CESs are required, they are universally recognized as the major cost driver of the 351(k) approval process.

To estimate the out-of-pocket cost for CESs, we applied a similar approach to that of PK/PD similarity studies. We acquired cost per subject information disaggregated by location and therapeutic area [30, 60] and multiplied these values by the respective sample size from Table 16 above. All subjects in CESs were assumed to be sick patients and the cost per subject data for CESs was assumed to represent cost per patient. Thus, no further adjustments were made to the data.

Table 18 below presents an example of the baseline estimates calculated for CESs, for an assumed study location of the United States. While costs vary by location, phase duration and transition success probability do not.

Table 18. Estimated Baseline Model Parameters for CESs, By Therapeutic Area

	Baseline Estimate
Hematology	
Out-of-Pocket Cost (in 2023 $) [a]	$82.6 million
Phase Duration (Mo) [c]	28.5
Transition Success Probability [b]	86.4%
Immunology	
Out-of-Pocket Cost (in 2023 $) [a]	$38.3 million
Phase Duration (Mo) [c]	28.5
Transition Success Probability [b]	86.4%
Oncology	
Out-of-Pocket Cost (in 2023 $) [a]	$58.9 million
Phase Duration (Mo) [c]	40.9
Transition Success Probability [b]	86.4%
Other	
Out-of-Pocket Cost (in 2023 $) [a]	$34.8 million
Phase Duration (Mo) [c]	28.5
Transition Success Probability [b]	86.4%

[a] Out-of-pocket costs shown here reflect those estimated for a CES program made up of exclusively healthy subjects located in the United States. These values are calculated as the average sample size (Table 16) multiplied by the cost per subject (obtained from Sertkaya et al. [30, 60]).
[b] Transition success probability was obtained from a report published by the Biotechnology Innovation Organization [61]. Biosimilar success rates were not disaggregated by therapeutic area or study characteristics and thus, we assume that 86.4% applies to all CES groups.
[c] Phase duration estimates represent the average of SME reported values.

4.1.3.4 Bridging Study

Frequently, a biosimilar sponsor uses a non-U.S.-licensed product in its clinical studies (e.g., a foreign-sourced version of the RP that has been approved and marketed in other jurisdictions, such as the EU, Japan, or Australia). Sponsors may do this to lower their costs or for convenience (if obtaining enough of the FDA-approved RP is problematic) [62]. When sponsors use a non-U.S.-licensed comparator, FDA requires evidence from a bridging study that this secondary RP behaves the same pharmacologically as the U.S.-licensed version. A bridging study usually comprises a series of comparisons of the non-U.S.-licensed comparator RP with the U.S.-licensed RP. FDA defines the "Comparability Bridging Study" as "A study performed to provide nonclinical or clinical data that allows extrapolation of the existing data from the drug product produced by the current process to the drug product from the changed process" [63]. Often, the bridging study constitutes a third arm in the PK/PD similarity study, which is the most cost-efficient approach. In some cases, the decision to use a non-U.S.-licensed comparator is made after PK/PD similarity studies are complete, and the bridging study is an additional PK/PD similarity study with two arms—one for the U.S.-licensed RP and another for the non-U.S.-licensed RP. In such scenarios, experts interviewed for this study judged that the average cost, duration, and success probability for a standalone bridging study are similar to those for a phase 1 study. Given the variation in the timing of bridging studies within phase 1 and their ability to be integrated with PK/PD studies, we calculated phase 1 average total sample sizes and total durations separately for those drugs with and without *any* bridging study.

4.1.3.5 Switching Study

When a biosimilar sponsor seeks interchangeability status, the sponsor may need to perform a switching study to show that switching from the RP to the biosimilar has no more risk in terms of safety or diminished efficacy as compared to continuing use of the RP.[25] Switching studies may require the use of RP in both the active switching arm and the control non-switching arm [5]. Therefore, the quantity of RP required may act as a barrier or as a major cost driver for those sponsors seeking interchangeability (Trade Group 2). In our data, which included five switching studies (Semglee, Cyltezo, Abrilada, Hadlima, and Yuflyma), we found that switching studies typically occurred towards the end of CES or after CES had been completed and that the sample size of switching studies was typically smaller than that of the average sample size for a CES of the same drug (Table 16).

4.1.3.6 Patent Litigation Phase

A biosimilar company can pursue FDA approval before the patents held by the RP expire. Unlike the Hatch Waxman Act, which restricts FDA from giving "final" approval to a generic drug until patent issues are resolved, BPCIA has effectively kept FDA from playing any

[25] Among seven interchangeables approved as of November 2023, only Cimerli (by Coherus Biosciences), which is interchangeable with Lucentis, was not required by FDA to perform a switching study. FDA stated that Coherus's application included "a comprehensive and robust analytical assessment that compared the structural and functional characteristics of Cimerli (ranibizumab-eqrn) to Lucentis (ranibizumab injection) and other clinical safety, immunogenicity, and effectiveness data, to support the FDA's determination that a switching study was not needed to support licensure of Cimerli as interchangeable to Lucentis" [160].

role in such litigation. In Hatch Waxman, once the brand drug company responds to the generic's paragraph IV certification that it intends to assert its patent rights, a 30-month hold is placed on FDA's approval process. In contrast, biosimilars pursuing FDA approval in the face of a patent-protected RP do not face any 351(k) application delay. When we look at the gap between the filing of patent litigation (or negotiation via the patent dance) and the launch of the biosimilar, we find that the litigation usually does not cause a delay in launch that exceeds 30 months.

Under BPCIA, FDA can approve the biosimilar for commercial distribution regardless of litigation status; the biosimilar, once approved, is free to enter the market at risk. It should be noted that the general trend is that the biosimilar companies are more successful in these patent disputes than the RPC. A singular exception is Abbvie's series of settlements with the numerous (nine approved so far) biosimilars seeking to compete with Humira. The first three Humira biosimilars, Amjevita (Amgen), Cyltezo (Boehringer-Ingelheim), and Hyrimoz (Sandoz) were approved in 2016, 2017, and 2018, respectively. All settled with Abbvie, agreeing to wait until 2023 to enter the U.S. market, and at least one, Amjevita, agreed to pay Abbvie a royalty for competing with them in the United States.[26] In Table 19, we present data on how long approved biosimilars have had to wait to enter the U.S. market from the time patent-related legal activity had begun, given different outcomes in court.

Table 19. Months from First Legal Action to Biosimilar Launch

Litigation Result	Sample Size (n)	Months from First Legal Action to Market Launch	
		Mean	Median
All eligible biosimilars	21	26.5	20.8
Settlement	11	32.3	21.9
Biosimilar wins	7	15.8	10.9
Reference product wins	3	Too little data to summarize; individual values shown below: [a] 120 (Eticorvo) [a] 144 (Erelzi) [b] 37.5 (Retacrit)	

[a] 120 and 144 months are individual delays for Eticorvo and Erelzi. In 2019, Enbrel's (Immunex) patents were judged "not invalid" by the district court, and Sandoz did not contest infringement; in 2021, the district court upheld two major Enbrel patents, ruled that Samsung Bioepis had infringed them, and issued a permanent injunction to Samsung preventing their market entry until Immunex's patents expire in 2029 [64].
[b] Amgen filed their infringement complaint against Retacrit in 2015 and in 2017 a federal jury awarded Amgen $70 million for Hospira's act of infringement, which was to stockpile commercial quantities of their biosimilar. Retacrit was approved in May 2018 and launched in November 2018 [64].

Theoretically, a settlement of litigation should reflect the relative strength of the arguments that each side can bring to bear in court, or at least the strength as perceived by each side. The inducement of an early entry into the EU market in exchange for several years

[26] Abbvie does have some follow-on patents that do not expire until the 2030s, but many observers considered that Abbvie's offer to license these biosimilars in the EU market as early as 2018 made the four-to-six-year delay in the U.S. launch tolerable for these three companies. (Hyrimoz (Sandoz) actually settled with Abbvie a few weeks before being approved by FDA).

delay in entering the U.S. market has arguably skewed the data on how long an approved biosimilar will be delayed in getting to market.

The first three companies that accepted Abbvie's unusual settlement offer caused a longer average gap between initial legal action and the launch of Humira biosimilars in the United States. To mitigate this effect, we did not include the subsequent six Humira biosimilars in our count of biosimilar litigants. This seemed reasonable because it was not clear that patent-related litigation had been filed naming any of these six Humira biosimilars. All were noted as having entered a licensing agreement with Abbvie, with launch dates in 2023.

The first three Humira biosimilars agreed to delays of 61.5, 70.8, and 77.7 months from the first patent-related legal filing before entering the Humira market in 2023. These were also the longest gaps between FDA approval and market entry. They drive up the average time to launch among biosimilars that had settled their litigations (n = 11) to 32 months, whereas without them, the average time to launch would have been 18 months.

There are several pathways the biosimilar may take if the RP is patent protected. Once they have submitted their 351(k) application, they may notify the RP company that they have done so, which indicates their willingness to participate in the patent dance. If the RP company agrees, they will engage in a well-scripted exchange of information and negotiation—colloquially called the patent dance—that can last about 254 days. Neither party is obligated to participate, nor to continue participation once started. The RP company may file an action alleging infringement, either in district court or at the Patent Trial and Appeal Board (PTAB). They can also ask the court for an injunction to prevent the biosimilar from entering the market, pending the outcome of litigation. The biosimilar will seek to have the major patents declared invalid, or to have the court rule that they have not infringed the patent(s) at issue.

There are several potential decision points before the issues get to study stage, and normally the parties will be negotiating throughout the process. For the purposes of the model, we assumed an overall average duration of 23.6 months to resolve all patent litigation issues.

4.1.3.7 FDA 351(k) Application Preparation and Submission Phase

FDA 351(k) Application User Fees

The Biosimilar User Fee Act (BsUFA) framework, which aligns with the Prescription Drug User Fee Act (PDUFA) in many ways, has distinct fee structures specifically tailored for biosimilars. The fees under BsUFA include:

- *Biosimilar Biological Product Development (BPD) Fees* – These are paid when a company enrolls in the BPD program. There are initial and annual BPD fees, as well as reactivation fees if the company had previously withdrawn from the program.
- *Application Fees* – These are paid when submitting an application for a biosimilar to FDA and vary based on whether clinical data are required or not.
- *Program Fees* – These are charged annually for each biosimilar product that is approved under a 351(k) application.

Unlike PDUFA, which includes application and program for originator pharmaceuticals, the BsUFA structure does not encompass these types of fees for biosimilars. This distinction

reflects the unique regulatory and developmental challenges associated with biosimilars compared to traditional pharmaceuticals. The BsUFA III fees are presented in Table 20.

Table 20. Industry User Fees under Biosimilar User Fee Amendments (BsUFA 3)

User Fee Type		FY 2023	FY 2024
Biosimilar BPD Fee	Initial BPD	$47,325	$10,000
	Annual BPD	$47,325	$10,000
	Reactivation	$94,650	$20,000
Application Fee [a]	Clinical Data Required	$1,746,745	$1,018,753
	Clinical Data not Required	$873,373	$509,377
Program Fee (annual)		$304,162	$177,397

BPD = biological product development
Source: U.S. Food and Drug Administration [65].
[a] Small companies (<500 FTEs) submitting their first application to license a human drug can apply to have the application fee waived.

Risk Evaluation and Mitigation System (REMS) Submission

FDA requires drugs that have the potential to cause serious or catastrophic adverse events if not properly prescribed, administered, or monitored to have a Risk Evaluation and Mitigation Strategy (REMS) that will "inform and/or support the safe use conditions described in the medication's FDA-approved prescribing information" [66]. If an RP is subject to REMS, the 351(k) application referencing that biologic is subject to the medication guide (MG) and Elements to Assure Safe Use (ETASU) requirements. Further, FDA requires that the 351(k) applicant "use a single, shared system (SSS) REMS with the innovator drug for any ETASU unless FDA waives this requirement, in which case the 351(k) submitter can use a different, but comparable system" [67]. Thus, any biosimilar version of an RP with a REMS must either negotiate to enter an SSS REMS with the innovator or develop and maintain its own REMS. The biosimilar applicant also needs to provide its REMS assessment to FDA during the BLA submission process or shortly thereafter.

In July 2024, FDA's listing of drug products with a REMS included 21 biologics (out of a total of 73 REMS drugs listed). Four of the biologics on the list are biosimilars (Tyruko, BKEMV, Epysqli, and Jubbonti).

Table 21 presents the different components that a REMS program can have. According to FDA data, as of December 2023, there were 18 shared system REMS programs, and all 18 have ETASU, 58 have an implementation system, 11 have a medication guide, and 8 have a communication plan component [68].

In recent years, brand drug companies have used the REMS system to delay biosimilar entry by (1) obstructing biosimilar companies from getting samples of the REMS brand drug for testing and (2) engaging in dilatory shared-REMS negotiations. FDA has acted to inhibit these obstructive activities, and they appear to have subsided somewhat recently [69].

Table 21. Components of a REMS Program [a]

REMS Component	Description
MG or Patient Package Insert	Provides FDA-approved patient-friendly labeling. Must meet requirements of 21 CFR 208: MG can be required if FDA determines one or more:

REMS Component	Description
	Patient labeling could help prevent serious adverse events The product has serious risks that could affect patient's decision to use or continue to use Patient adherence to directions is crucial to product effectiveness
Communication Plan for Healthcare Providers	FDA-approved materials used to aid sponsor's implementation of REMS and/or inform healthcare providers about risks
ETASU	Depending on the risk, a REMS may require any or all of the following: Certification or specialized training of HCPs who prescribe the drug. Certification of pharmacies or other dispensers of the drug. Dispensing/administration of drug in limited settings e.g., hospitals. Dispensing/administration of drug only with evidence of safe-use conditions. Each patient using the drug is subject to certain monitoring Enrollment of treated patients in registries.
Implementation System	REMS may include an implementation system related to the following ETASU: Certification of pharmacies and hospitals Healthcare settings Safe use conditions May require applicant to take reasonable steps to: Monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements; and Work to improve implementation of such elements by such persons

REMS = Risk Evaluation and Mitigation Strategy
MG = medication guide
ETASU = Elements to Assure Safe Use
Source: Lippmann [67]
[a] Not all REMS programs have all of these components; some, for example, just consist of MG and ETASU.

The cost of a shared or new REMS program is expected to vary significantly, as these programs differ in their complexity and entail both origination and maintenance costs.[27] REMS programs with an ETASU and/or implementation system appear to be the most onerous to set up and operate, and thus are likely to impose a higher burden on the biosimilar company. However, as more companies join an SSS, the set-up and maintenance costs of the program would be shared across all participants, lowering this burden on each individual participant. There are also independent contractors specializing in the design and maintenance of REMS so smaller biosimilar companies that may not have expertise in this area are not necessarily shut out.

FDA 351(k) Application Process

Upon receipt of the 351(k) application and payment of the BsUFA III application fee, the biosimilar company faces one of three outcomes:

- *Approval* – If FDA deems that the 351(k) submission meets the substantive requirements for approval, it issues an approval letter to the applicant, regardless of any unresolved patent issues facing the applicant.

[27] REMS may also require different BE study protocols. For instance, if REMS prevent prescribing to women that may become pregnant, a company may decide to only enroll males instead in their clinical trials.

- *A refuse-to-file (RTF) decision* – An RTF decision indicates that the 351(k) application is not sufficiently complete to enable a substantive review by the FDA [70]. (Section 744B(a)(3)(D)(i) of the FD&C Act).
- *A Complete Response Letter (CRL)* – A CRL lays out FDA's review of the 351(k) application and the subsequent finding that it cannot approve the application in its present form under (21 CFR §601.3(a)). A CRL describes the reasons for finding the 351(k) submission inadequate and may include recommendations on how the submitter needs to address the identified deficiencies, which could be minor or major. The 351(k) submitter then can amend the application and seek another full FDA review, withdraw its application, or, in some cases, not respond. Upon receipt of a resubmission, FDA reviews changes made to the 351(k) application in response to deficiencies identified and can either approve the application or issue another CRL.

FDA Pre-license Inspection

When the 351(k) application is deemed approvable, FDA may conduct a pre-license inspection (PLI) of the facility that will be manufacturing the finished dosage form. The goal of a PLI is ensure that the manufacturing establishment named in the BLA is in fact capable of manufacturing the drug, and that the data submitted in the 351(k) application's chemistry, manufacturing, and controls (CMC) section are accurate and complete [71]. We assume that the PLI would add $20,000 in cost and eight months to the development timeline, based on best professional judgment.

4.2 Analytical Framework for Revenues

Our revenue model estimates the lifetime net sales earned by a manufacturer of a biosimilar product.[28] Parts of this approach are described by McGeeney et al. [72]. We applied this model to CDER biologics that do not currently have biosimilar competition but might serve as RPs in the future. We approximated a biosimilar's lifetime in the market using a 10-year post-launch period, which is longer than any existing biosimilar had been on the U.S. market as of the time of analysis and required forecasting trends. Therefore, we A) developed mathematical functions that follow the trends in existing biosimilars' net sales in the United States, B) applied those functions to the markets of biologics that do not currently have biosimilar competition, and C) extrapolated those functions to a 10-year projection period.

Section 4.2.1 describes the inclusion criteria for the trend analysis of existing biosimilars' net sales. Section 4.2.2 discusses the functions we developed for characterizing trends in existing biosimilars' net sales. Section 4.2.3 explains how those functions were applied to new CDER biologics that might serve as RPs in the future.

4.2.1 Inclusion Criteria for Revenue Trend Analysis

We selected six U.S. biologics markets with biosimilar competition for the net sales trend analysis: bevacizumab, filgrastim, infliximab, pegfilgrastim, rituximab, and trastuzumab. To be selected for our study, a market had to have two or more biosimilars each with at least

[28] By using net sales, we account for most price concessions manufacturers make, such as discounts and rebates to supply chain intermediaries. This does not, however, account for the cost of goods, which we did not estimate.

two years of net sales data. This criterion excluded the markets for adalimumab, which had nine biosimilars launched in 2023; ranibizumab, with two biosimilars launched in June and October 2022; and insulin glargine, which had a second biosimilar launched in April 2023. While we only fit models for biosimilar products with at least two years of sales data, we accounted for the net sales of all biosimilar entrants (even those with fewer than two years of data) when calculating the modeled products' market shares.

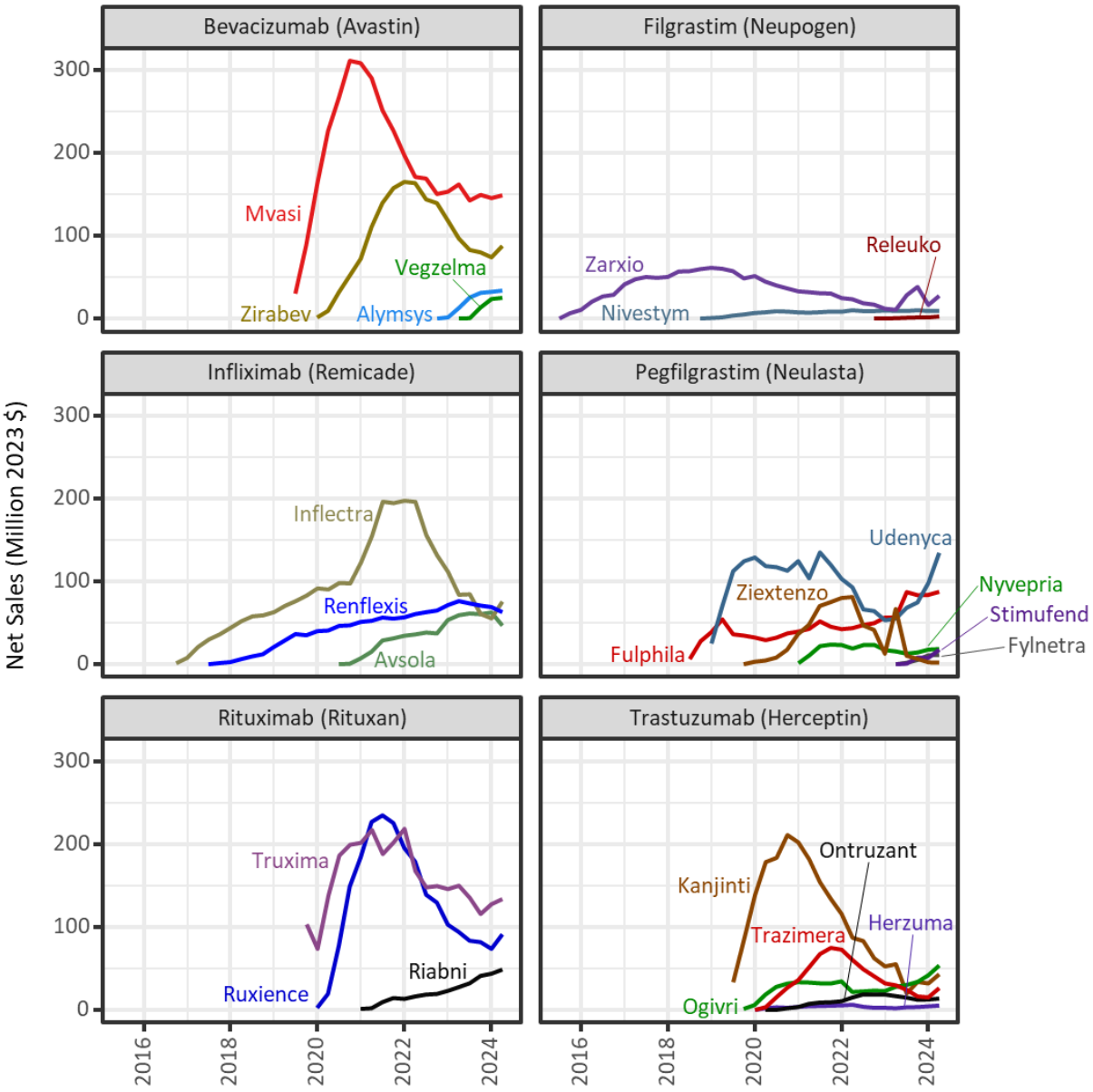
We imposed this inclusion criterion because our study requires estimating the manufacturer's net sales over a 10-year post-launch period. The accuracy and precision of these 10-year estimates increase when the projections are based on longer periods of observed sales data.[29] In addition, we found that it took a minimum of roughly two years for competitive dynamics involving biosimilars to begin to stabilize. Two years after the first biosimilar product's entry date, there tended to be far fewer additional biosimilar entrants, and market shares tended to approach a more well-defined equilibrium.

4.2.2 Estimating Lifetime Revenues of Existing Biosimilar Products

For a biosimilar product, the trend in net sales is difficult to model because it is nonmonotonic and lacks a well-defined functional form. In general, we observed that a biosimilar product's net sales increase rapidly toward a peak and then decrease more slowly. As Figure 4 shows, however, there is wide variation across biosimilar products.

[29] All of the included biosimilar products had at least 14 quarters of data (i.e., 3.5 years). Thus, the 10-year projections involved extrapolating the net sales over roughly twice the duration of observed data, at most.

Figure 4. Quarterly Net Sales for U.S. Biosimilar Products



Note: Graph shows the quarterly U.S. net sales of all approved biosimilars in the six markets we modeled. Net sales are estimated using volume sales data from IQVIA NSP and pricing data from both IQVIA NSP and CMS ASP pricing files.

The complicated trend in net sales is the result of several simpler underlying market dynamics: (1) after biosimilar entry, the RP loses market share; (2) later biosimilars compete not only with the RP but also with earlier biosimilars; (3) the increased competition causes prices to drop, which tends to occur more rapidly at the beginning of biosimilar competition and can lead to more utilization of the drug [72]. We therefore decomposed the biosimilar net sales trend into three separate functions that are simpler and monotonic; are based on more fundamental and predictable market dynamics; and are amenable to "what if" scenario modeling, which we used to assess the impact of possible policy incentives.

Some parts of the net sales trend analysis use market shares, which requires predefined markets. We define the "total market" to include a U.S. RP and all of its biosimilars that have launched in the United States. This definition is consistent with the interviewed biosimilar developers' notion of a "market" [51].[30] We also consider the "biosimilar market," which we define to include only the biosimilar products without their corresponding RP. Using this framework and the steps below [72], we estimated the trend in net sales of an existing biosimilar product.

1. **Fit a decay model to estimate the trend in total market net sales after entry of the first biosimilar product.** The selection of a decay model is justified by the fact that biosimilar entry leads to greater competition and declining prices, which in turn cause net sales to decline. We observed this pattern in all six U.S. markets with biosimilar competition that we included in the study.
2. **Calculate the share that all biosimilars earn, combined, of the total market's net sales. Fit a monotonically increasing growth model to estimate the trend in the biosimilars' aggregate market share.** The use of a growth model is justified by the fact that biosimilars start with no market share, which increases over time as more biosimilar products enter and as healthcare providers update their contracts and formularies to include biosimilars. We used a monotonically increasing function because biosimilar adoption tends to increase over time as providers become more comfortable with the product, and it is less common for providers to switch back to the RP (which is more expensive) after adopting a biosimilar that performs equally well. After some time, the market saturates and biosimilars achieve their maximum market penetration. Some patients and providers never switch to a biosimilar product due to brand loyalty or favorable contracts (bundling of the RP with other drugs, rebates offered by the RP manufacturer, etc.).
3. **For each biosimilar product in the market, fit a model to estimate the trend in that product's share of the biosimilar market's net sales.** For the first biosimilar entrant, we used a monotonically decreasing function because the first mover starts with 100 percent share of the biosimilar market's net sales, which then decreases as other biosimilar products launch. For later biosimilar entrants, we used a monotonically increasing function in almost every case because later entrants start with no share of the biosimilar market, which then increases until they reach their maximum market penetration.

In the remainder of this section, we describe each of these three steps in detail, and we present the fitted models.

[30] Alternate definitions of a market may include other 351(a) original biologics with the same or a similar molecule but are not listed as an RP on any biosimilar applications. While we excluded these "other 351(a) products" from our narrower definition of a market, our model captures their impact, to the extent that these products affect a biosimilar product's net sales.

4.2.2.1 Step 1: Total Market Net Sales after Biosimilar Entry

First, we estimated the total net sales for each included market, on a quarterly basis, from initial biosimilar entry through Q2 2024. We used the NSP dataset published by IQVIA and the Average Sales Price (ASP) files published by the Centers for Medicare & Medicaid Services (CMS). IQVIA's NSP dataset is a nationally representative survey of manufacturer and wholesaler invoices to healthcare providers with information on total packages sold and the average invoice price paid by healthcare providers to the manufacturer or wholesaler. The CMS ASP pricing files provide Medicare reimbursement rates, from which we calculated manufacturers' net prices [73, 74]. In each quarter, we estimated the manufacturer's net price for a given product as the minimum of the ASP and the IQVIA NSP invoice price. To compute a product's net sales in a given quarter, we multiplied the manufacturer's net sales price by the total packages sold according to IQVIA NSP. We then summed the net sales for all products in a given market to acquire the net sales of the total market.

For each of the six selected U.S. markets, we fit a modified exponential decay function to the trend in total market net sales, $R_{t,i}^{*}$. We used exponential decay functions because, upon entry of a biosimilar product, the net sales $R_{t,i}^{*}$ decline due to decreasing prices[31] and then approach an asymptote representing the long-run steady-state quarterly sales. Equation 7 shows the form of this decay function. The variable t represents the number of years since biosimilar entry and the variables A_i, B_i, C_i, and D_i represent model parameters to be estimated.

$$R_{t,i}^{*} = A_i + B_i \exp(-C_i \cdot t^{D_i}) \quad (7)$$

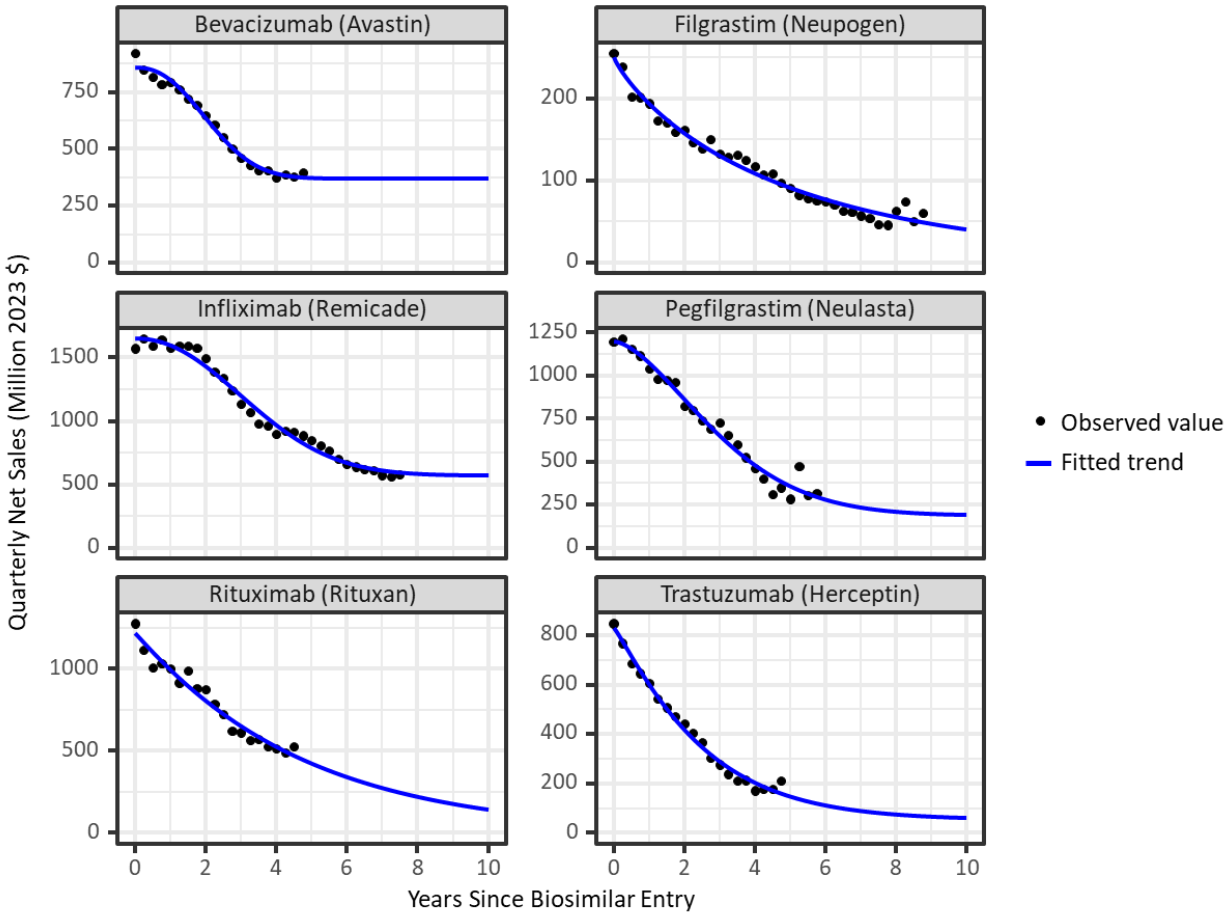
Parameter A_i is the total market's long-run steady-state quarterly net sales after biosimilar entry. Parameter B_i is the difference between RP's net sales just before biosimilar entry and the long-run steady-state quarterly net sales A_i. Parameter B_i can be interpreted as the total decline in quarterly net sale dollars due to biosimilar entry. Parameter C_i is a decay constant that quantifies the rate at which net sales decrease over time. We refer to parameter D_i as the slope constant, which is included to allow for slower initial reduction in total net sales when the first biosimilar entrant is beginning to gain market share.[32] We added the parameter D_i to account for the fact that some U.S. markets experienced slower initial reduction in net sales after biosimilar entry. For example, see infliximab and pegfilgrastim in Figure 5 below. One advantage of using exponential decay functions is that the market size just before biosimilar entry is equal to the sum of A_i and B_i, which facilities projections for new RPs that do not yet have biosimilar competition, as discussed in greater detail in Section 4.2.3. When fitting these decay models, we constrained the parameter A_i (long-run steady-state quarterly net sales) to be greater than zero since net sales cannot be negative. We constrained the parameter C_i (decay constant) to be less than zero because net sales decrease after biosimilar entry.

[31] In some cases, the decreasing prices are partially offset by increasing volume sales, but the net effect is that total net sales decrease in all of the markets we examined.

[32] This mirrors the form of the logistic growth functions (discussed below) that model biosimilars' share of total net sales.

Figure 5 shows the net sales and the fitted exponential trends for the six U.S. markets we analyzed. Table 22 shows the estimated model parameters for each fitted model in Figure 5. We assessed the model's goodness of fit using the Akaike information criterion (AIC), the Efron pseudo R^2 statistic, and the p value for an F test comparing the fitted model to an intercept-only null model. All models had very good fits based on these statistics. In Table 22, we also present standard errors for the fitted model parameters.

Figure 5. Estimated Exponential Decay Functions for Total Market Net Sales



Note: Graph shows quarterly U.S. net sales for the total market, which includes all biosimilars and the RP they name on their 351(k) applications. Graph only includes the six U.S. markets with at least two biosimilars each with at least two years of sales data. Years since biosimilar entry varies by market because some markets have had biosimilar competition for more years than others. Net sales are estimated using volume sales data from IQVIA NSP and pricing data from both IQVIA NSP and CMS ASP pricing files.

Table 22. Estimated Model Parameters for Total Market Revenues after Biosimilar Entry, by Market

Market	Long-run Quarterly Sales (Million 2022 $), A_i	Decline in Sales due to Biosimilar Entry, B_i	Decay Constant, C_i	Slope Constant, D_i	Goodness of Fit Statistics
Bevacizumab (Avastin)	3.69×10^8 SE = 1.83×10^7 p < 0.001	4.86×10^8 SE = 2.58×10^7 p < 0.001	-0.120 SE = 0.028 p < 0.001	2.346 SE = 0.277 p < 0.001	p < 0.001 R^2 = 0.986 SSE = 9.35×10^{15} AIC = 742
Filgrastim (Neupogen)	0.00 SE = 2.76×10^6 p = 1.000	2.50×10^8 SE = 9.19×10^6 p < 0.001	-0.256 SE = 0.030 p < 0.001	0.848 SE = 0.058 p < 0.001	p < 0.001 R^2 = 0.978 SSE = 2.48×10^{15} AIC = 1,259
Infliximab (Remicade)	5.67×10^8 SE = 4.28×10^7 p < 0.001	1.09×10^9 SE = 5.74×10^7 p < 0.001	-0.052 SE = 0.014 p < 0.001	2.135 SE = 0.218 p < 0.001	p < 0.001 R^2 = 0.984 SSE = 7.63×10^{16} AIC = 1,197
Pegfilgrastim (Neulasta)	1.86×10^8 SE = 1.29×10^8 p = 0.163	1.01×10^9 SE = 1.48×10^8 p < 0.001	-0.132 SE = 0.029 p < 0.001	1.618 SE = 0.281 p < 0.001	p < 0.001 R^2 = 0.975 SSE = 5.65×10^{16} AIC = 928
Rituximab (Rituxan)	3.44×10^2 SE = 8.38×10^8 p = 1.000	1.22×10^9 SE = 8.38×10^8 p = 0.167	-0.203 SE = 0.147 p = 0.187	1.027 SE = 0.299 p = 0.004	p < 0.001 R^2 = 0.959 SSE = 4.21×10^{16} AIC = 735
Trastuzumab (Herceptin)	5.20×10^7 SE = 7.59×10^7 p = 0.503	7.79×10^8 SE = 8.68×10^7 p < 0.001	-0.349 SE = 0.038 p < 0.001	1.117 SE = 0.138 p < 0.001	p < 0.001 R^2 = 0.990 SSE = 8.96×10^{15} AIC = 741

SE = Standard error; SSE = Sum of squares error; AIC = Akaike information criterion; R^2 = Efron pseudo R^2 statistic; p value is for an F-test comparing the residual sum of squares of the fitted model to a null model with just the intercept term.

Notes: net sales are estimated using volume sales data from IQVIA NSP and pricing data from both IQVIA NSP and CMS ASP pricing files. The parameters presented in this table were used to estimate the trend in U.S. net sales of the total market, which includes al biosimilars and the RP they name on their 351(k) applications. We only analyzed six markets that had at least two biosimilars each with two or more years of sales data. The equation for estimating the trend in net sales of the total market is: $R_t^* = A_i + B_i \exp(-C_i \cdot t^{D_i})$.

4.2.2.2 Step 2: Estimating Share of Total Revenues for Biosimilars

Next, we estimated the share $s_{t,i}$ of total net sales that all biosimilars in a market will earn, combined. We refer to this as the "combined biosimilar market share." For each of the six U.S. markets, we calculated the fraction $s_{t,i}$ of total net sales that the biosimilar products earned in each quarter after first biosimilar entry. We fit logistic growth functions to the combined biosimilar market share $s_{t,i}$. We selected logistic growth functions because biosimilars start with no market share, which increases as providers adopt biosimilar products and update their supplier contracts. The market share eventually reaches a peak; some providers and patients continue to use the RP due to brand loyalty, favorable contracts, etc. We observed this same increasing trend in combined biosimilar market share $s_{t,i}$ in all U.S. markets that we included in

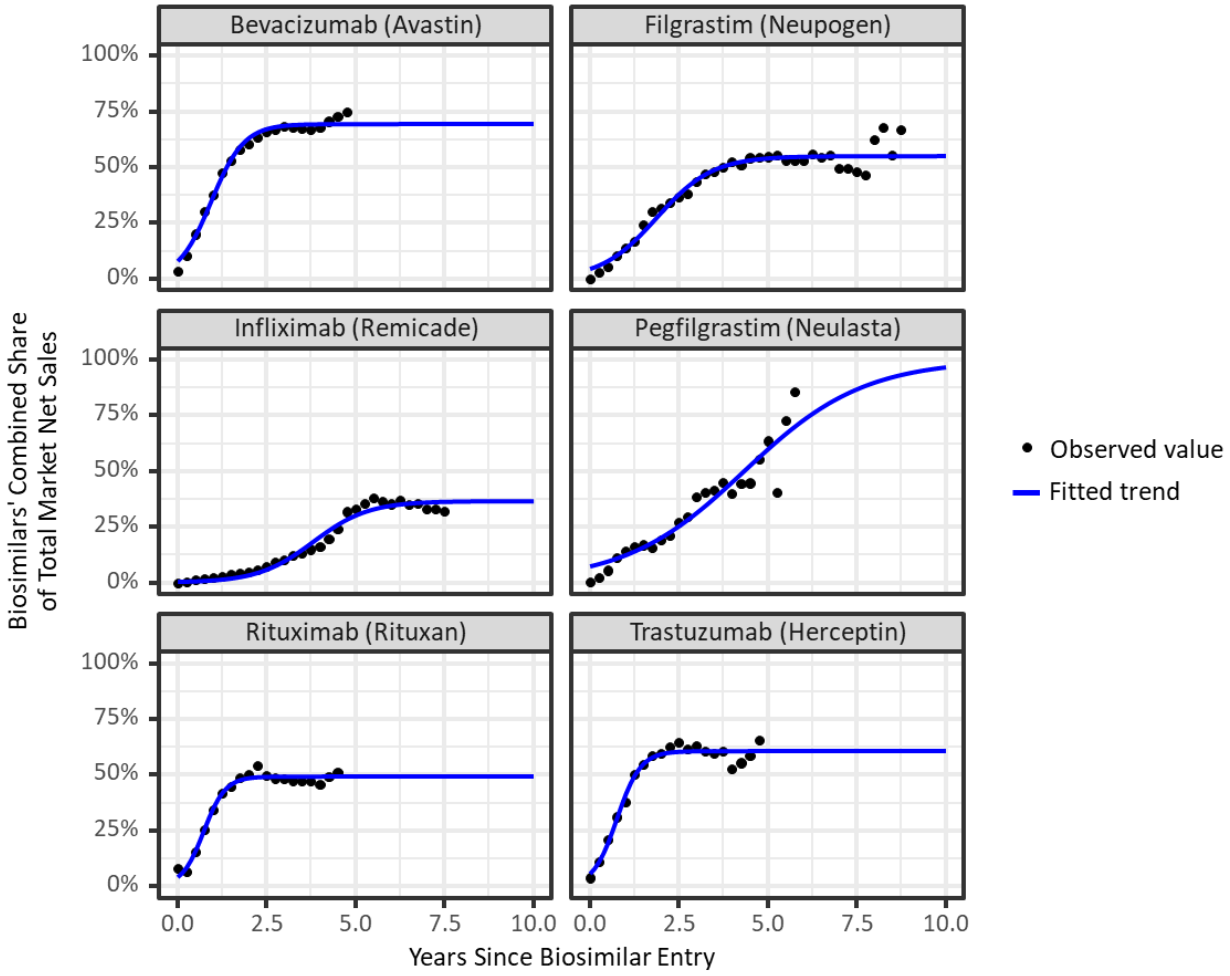
our study, making the logistic growth function a good fit. The model specification for the logistic growth function is [72]:

$$s_{t,i} = \frac{s_{\max,i}}{1 + \exp\left(\frac{t_{0,i} - t}{k_i}\right)} \quad (8)$$

In equation 8, $s_{max,i}$ is the long-run peak share of total net sales that the biosimilar products earn in aggregate, k_i is the biosimilar market share growth rate, and $t_{0,i}$ is the midpoint of the logistic growth function (i.e., the point at which the market share has reached half of $s_{max,i}$). The fitted logistic growth functions for each of the seven U.S. markets are shown below in Figure 6, along with the observed net sales data.

Table 23 presents the fitted parameter estimates for the logistic growth functions for each of the six U.S. markets. There is substantial variation across markets in the projected long-run share $s_{max,i}$ of total revenues that the biosimilar products will earn, ranging from 36.7 percent (infliximab) to 69.1 percent (bevacizumab). The combined biosimilar market share has a long-run value of 100 percent for filgrastim, but this estimate is highly uncertain, as indicated by the large standard error of 33.6 percent. The growth midpoint $t_{0,i}$ is smaller in markets where biosimilars approached the long-run maximum market share $s_{max,i}$ more quickly, such as bevacizumab, rituximab, and trastuzumab. We used sum of squared error (SSE), the Efron pseudo R^2 statistic, and AIC to assess the model's goodness of fit. We also calculated standard errors for the model coefficients. The models generally achieved good fits, but in the case of pegfilgrastim, the standard errors and uncertainty are higher due to wider fluctuations in the biosimilar market share in recent years, including more rapid growth in 2024.

Figure 6. Estimated Logistic Growth Functions for Total Biosimilar Market Shares



Note: Graph shows uptake of market share by all biosimilars combined in their respective markets, each of which includes the biosimilars and the RP listed on their 351(k) applications. Market share is measured using net sales, which are estimated using volume sales data from IQVIA NSP and pricing data from both IQVIA NSP and CMS ASP pricing files. Graph only includes the six U.S. markets with at least two biosimilars each with at least two years of sales data.

Table 23. Estimated Model Parameters for Biosimilars' Combined Market Share

Market (Molecule and RP)	Maximum Market Share of all Biosimilars, $s_{max,i}$	Growth Midpoint, $t_{0,i}$	Growth Rate, k_i	Goodness-of-Fit Statistics for Full Model
Bevacizumab (Avastin)	69.1% SE = 0.8% p < 0.001	0.938 SE = 0.034 p < 0.001	0.460 SE = 0.032 p < 0.001	SSE = 0.010 AIC = -86.3 R^2 = 0.988
Filgrastim (Neupogen)	55.2% SE = 1.1% p < 0.001	1.873 SE = 0.099 p < 0.001	0.784 SE = 0.091 p < 0.001	SSE = 0.065 AIC = -117.4 R^2 = 0.944
Infliximab (Remicade)	36.7% SE = 1.2% p < 0.001	3.806 SE = 0.105 p < 0.001	0.776 SE = 0.085 p < 0.001	SSE = 0.018 AIC = -134.8 R^2 = 0.97

Market (Molecule and RP)	Maximum Market Share of all Biosimilars, $s_{max,i}$	Growth Midpoint, $t_{0,i}$	Growth Rate, k_i	Goodness-of-Fit Statistics for Full Model
Pegfilgrastim (Neulasta)	100% SE = 33.6% p = 0.007	4.333 SE = 1.237 p = 0.002	1.682 SE = 0.439 p < 0.001	SSE = 0.115 AIC = -52.1 R^2 = 0.897
Rituximab (Rituxan)	49.2% SE = 0.7% p < 0.001	0.729 SE = 0.033 p < 0.001	0.303 SE = 0.030 p < 0.001	SSE = 0.008 AIC = -86.0 R^2 = 0.98
Trastuzumab (Herceptin)	60.6% SE = 0.9% p < 0.001	0.755 SE = 0.040 p < 0.001	0.331 SE = 0.037 p < 0.001	SSE = 0.017 AIC = -76.4 R^2 = 0.974

SE = standard error; SSE = sum of squared errors; AIC = Akaike information criterion; R^2 = Efron pseudo R^2 statistic.
Note: Table shows parameters for fitted logistic growth functions, which model the uptake of market share that biosimilars earn in the aggregate in their respective markets. A market includes the biosimilars and the RP they list on their 351(k) applications. Table only includes the six U.S. markets with at least two biosimilars each with at least two years of sales data. Market share is calculated from net sales, which are estimated using volume sales data from IQVIA NSP and pricing data from both IQVIA NSP and CMS ASP pricing files.

4.2.2.3 Step 3: Estimating Market Share for a Biosimilar Entrant Based on Order of Entry

For an individual biosimilar product with entry order n, we modeled its share $b^{(n)}_{t,i}$ of the biosimilar market i at each time t (measured in years) after the product launched. We used a different model specification for first movers into the biosimilar market (equation 9) than for later biosimilar entrants (equations 10 and 11) because first movers' share of the biosimilar market decreases over time whereas later entrants' market share increases. Due to the requirement for at least two years of data, our sample only included first through fifth biosimilar entrants.

For the first biosimilar entrant (n = 1), we modeled the share $b^{(1)}_{t,i}$ of the biosimilar market using a modified exponential decay function (equation 9) [72]:

$$b^{(1)}_{t,i} = b^{(1)}_{\max,i} + \left(1 - b^{(1)}_{\max,i}\right)\exp(-C_i \cdot (t_i + 0.25)^{D_i}) \quad \text{for } n = 1 \tag{9}$$

where i is the market, $b^{(1)}_{t,i}$ is the first biosimilar product's share of the biosimilar market, $b^{(1)}_{\max,i}$ is the product's long-run steady-state share of the biosimilar market, C_i is a decay constant, t_i is the time in years since entry of the second biosimilar, and D_i is a slope parameter that allows for slower initial decline in the first mover's biosimilar market share. Equation 10 is specified so that, in the quarter immediately before the second biosimilar enters (at t_i = -0.25), the first entrant's share of the biosimilar market is 100 percent.

For each later biosimilar entrant (n > 1), other than Udenyca (pegfilgrastim-cbqv) and Ziextenzo (pegfilgrastim-bmez), we used a logistic growth function to model the product's share of the biosimilar market, $b^{(n)}_{t,i}$ [72]:

$$b^{(n)}_{t,i} = \frac{b^{(n)}_{\max,i}}{1 + \exp\left(\dfrac{T^{(n)}_{0,i} - t^{(n)}_i}{K^{(n)}_i}\right)} \quad \text{for } n > 1 \tag{10}$$

In equation 10, $b^{(n)}_{\max,i}$ is the product's long-run steady-state share of the biosimilar market, K_i is the growth rate, and $T_{0,i}$ is the growth midpoint.

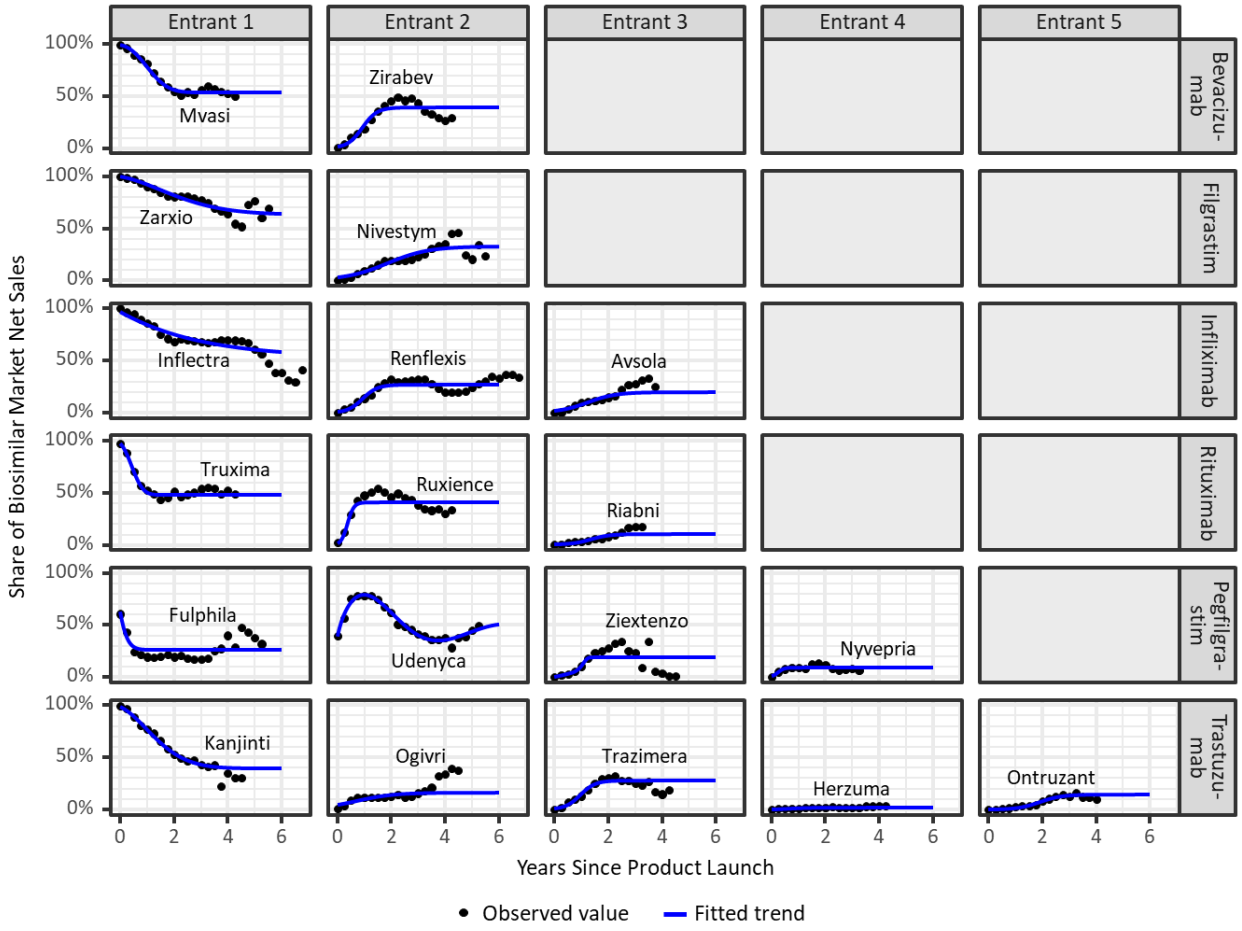
For Udenyca (pegfilgrastim-cbqv) and Ziextenzo (pegfilgrastim-bmez), we used the specification below (equation 11) that allowed the market share to overshoot the steady-state value because these two products exhibited extreme non-monotonic trends; for both products, the market share increased toward a peak and then decreased to less than 50 percent of that peak. The function below allows for damped oscillation around the steady-state market share [72]:

$$b_{t,i}^{(n)} = b_{\max,i}^{(n)} - a_i^{(n)} \exp\left(-c_i^{(n)} t_i^{d_i^{(n)}}\right) \cdot \cos\left(f_i^{(n)} t_i^{(n)} - g_i^{(n)}\right) \quad (11)$$

where $b^{(n)}_{\max,i}$ is the long-run steady-state market share and $a^{(n)}_i$, $c^{(n)}_i$, $d^{(n)}_i$, $f^{(n)}_i$, and $g^{(n)}_i$ are parameters to estimate.

For each market, we fit the models of all products' share of the biosimilar market simultaneously as a single equation with indicator variables for each distinct product. In markets where we modeled all biosimilar entrants (infliximab, rituximab, and trastuzumab), we constrained the sum of the long-run steady-state market shares to equal 100 percent. Figure 7 shows the resulting fitted models for each of the individual biosimilar products. The corresponding model parameters and goodness of fit statistics are presented in APPENDIX C: INDIVIDUAL BIOSIMILAR PRODUCT MARKET SHARE PARAMETERS.

Figure 7. Fitted Models for Individual Biosimilar Product's Share of Biosimilar Market



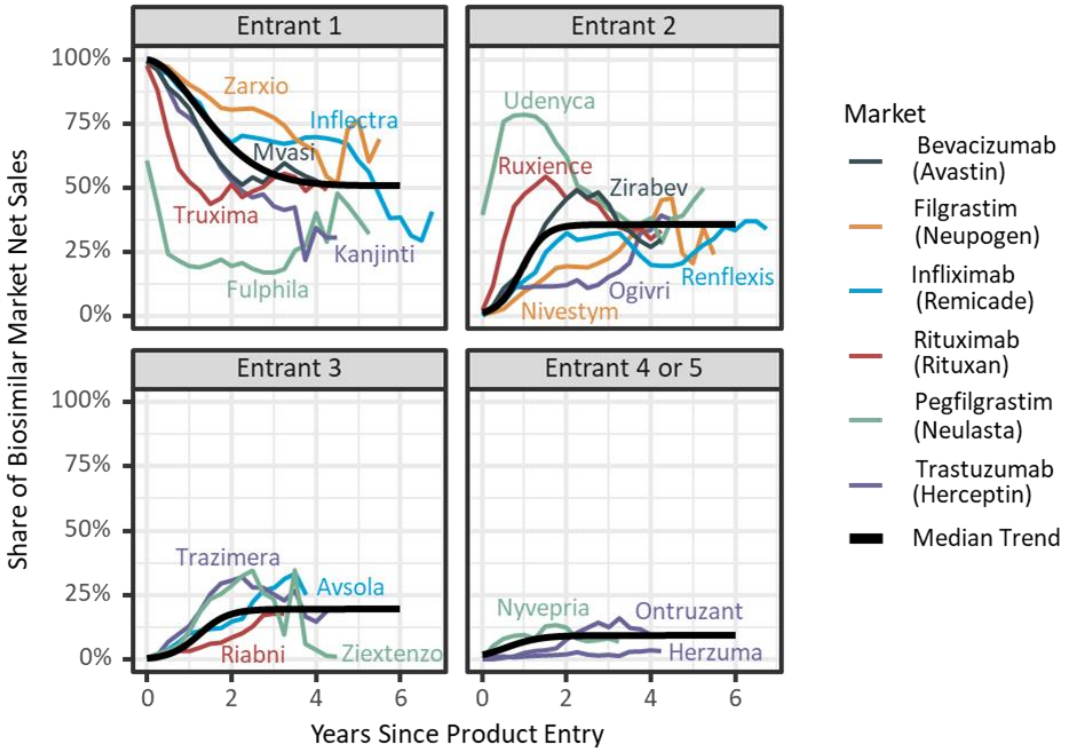
Note: Figure shows fitted growth or decay functions, which model the change in market share of individual biosimilars in their respective biosimilar markets. For first movers, the x-axis shows years since the second biosimilar launched. We define a biosimilar market to include only the biosimilar products without their RP. Figure only includes the six U.S. markets with at least two biosimilars each with at least two years of sales data. Market share is calculated from net sales, which are estimated using volume sales data from IQVIA NSP and pricing data from both IQVIA NSP and CMS ASP pricing files. Model parameters and goodness of fit statistics are presented in APPENDIX C: INDIVIDUAL BIOSIMILAR PRODUCT MARKET SHARE PARAMETERS.

Research suggests that earlier entrants into a pharmaceutical market generally capture a larger market share than later entrants, and this early-mover advantage can remain for years after launching [75]. According to one expert we interviewed, switching patients and providers from an existing biosimilar to a new biosimilar product is much more difficult than switching them from the RP to a biosimilar product because later biosimilar products enter the market after prices have declined and have less capacity to offer price reductions than earlier biosimilar entrants [51]. Early biosimilar entrants also earn higher sales revenues because they reap the benefit of the "market formation" period when prices are still on the decline from their pre-biosimilar-competition levels toward their long-run steady-state values. Later entrants into a market do not benefit from these early higher prices, which results in lower sales revenues [51].

Our findings are consistent with research and expert opinion. The fitted models of Figure 7 show that first entrants have higher long-run shares of the biosimilar market, in

general, followed by second entrants, then third entrants, and finally fourth or fifth entrants. This is also visible in Figure 8, which groups the biosimilar products by entry order and shows a median trend calculated using median parameters of each group of fitted models.

Figure 8. Median Trends for Individual Product's Share of Biosimilar Market, by Entry Order



Note: Figure shows change in market share for individual biosimilars in their respective biosimilar markets. For first movers, the x-axis shows years since the second biosimilar launched. We define a biosimilar market to include only the biosimilar products without their RP. Graph only includes the six U.S. markets with at least two biosimilars each with at least two years of sales data. Products are colored by market and grouped in panels by entry order. Market share is calculated from net sales, which are estimated using volume sales data from IQVIA NSP and pricing data from both IQVIA NSP and CMS ASP pricing files. The black trendline uses median model parameters for biosimilar products with that entry order. Because Udenyca and Ziextenzo were not modeled using logistic growth functions, they only contribute to the median long-run market share and not the other parameters.

Due to data limitations, we only modeled a maximum of five biosimilars in a single market. We also combined the results of fourth and fifth entrants because of small sample size. While this limits our analysis to first through fifth entrants, the number of biosimilars a given market can sustain is finite and is dependent on market size among other factors. According to industry experts, most markets cannot sustain more than five biosimilars, consistent with our analysis. Experts elaborated that oversaturated markets would lead to an unsustainable rate of market erosion and that early biosimilar markets have shown a "winner-takes-all" dynamic that precludes a large number of biosimilars to co-exist sustainably. Those markets in which annual RP revenues exceed $1 billion prior to biosimilar entry are generally a safe investment and can sustain multiple biosimilars. Markets in which annual RP revenues range from $500 million to $1 billion are riskier to enter but entry can be justified depending on market dynamics and the biosimilar developer's expertise and existing partnerships [51].

4.2.3 Estimating Lifetime Revenues of New Biosimilar Products

Section 4.2.2.1 describes the model for predicting net sales in the total market after biosimilar entry, $R^*_{t,i}$ (see equation 7). Section 4.2.2.2 describes the model for predicting all biosimilars' combined share of net sales in the total market, $s_{t,i}$ (see equation 8). Section 4.2.2.3 describes the model for predicting an individual biosimilar product's share of net sales in the biosimilar market, $b^{(n)}_{t,i}$ (see equations 9, 10, and 11). Multiplying these three quantities yields the biosimilar's predicted net sales over time.

$$R^{(n)}_{t,i} = R^*_{t,i} \times s_{t,i} \times b^{(n)}_{t,i} \tag{12}$$

$$R^{(n)}_{t,i} = (A_i + B_i \exp(-C_i \cdot t^{D_i})) \times s_{t,i} \times b^{(n)}_{t,i} \tag{13}$$

As stated previously, the sum of the parameters *A* and *B* approximates the total market's net sales before biosimilar entry. Therefore, to apply these equations to a possible future biosimilar of a new RP, *k*, we scaled the parameters *A* and *B* based on the new RP's current market size (i.e., current net sales), M_k, relative to the originally modeled RP's market size, *A* + *B*. The net sales are conditional on the biosimilar product's entry order, *n*, which is preselected by the user of the model.

$$R^{(n)}_{t,i} = \left(A_i \cdot \frac{M_k}{A_i + B_i} + B_i \cdot \frac{M_k}{A_i + B_i} \cdot \exp(-C_i \cdot t^{D_i})\right) \times s_{t,i} \times b^{(n)}_{t,i} \tag{14}$$

Equation 14 allows us to apply the fitted functions of any of the six modeled markets, *i*, to any other biologics market, *k*, that does not yet have biosimilar competition. It also allows us to project revenues over a 10-year post-launch period, with *t* = 0 years representing the first quarter of biosimilar entry and *t* = 9.75 years representing the final quarter of the biosimilar's marketing lifetime.

In our model, for a given biologic market, *k,* and a given entry order, *n*, we applied equation 14 for all observed markets, *i*, that have a biosimilar entrant with the selected entry order, *n*. Then, we averaged all of the resulting net sales estimates $R_{t,i}{}^{(n)}$:

$$R^{(n)}_t = \frac{1}{N} \sum_i R^{(n)}_{t,i} \tag{15}$$

In equation 15, *N* represents the number of estimates, i.e., the number of observed markets with a biosimilar of entry order *n*. The value of $R_t{}^{(n)}$ served as our estimate of the net sales, or revenues, at time point *t* for the biosimilar of selected market *k* and with selected entry order *n*.

4.3 Calculating Expected Net Present Value

The ENPV compares the lifetime costs to the lifetime revenues. A positive ENPV means a biosimilar product is a profitable endeavor, overall. Because the stream of costs does not occur at the same time as the stream of revenues, these amounts must be converted to present values. The possibility of failure also must be considered when comparing costs to revenues, which we do using expected values. Below, we present these calculations, which follow the framework of DiMasi et al. [53, 52, 50]. As was done by DiMasi et al. [53, 52, 50] our analysis is

also conditional on a biosimilar making it to market, and that estimates are not ENPV from the point of view of the start of development when it is unclear whether the compound will make it to market. The approach was adopted to maintain comparability with other published studies on cost of drug development.

The ENPV is the difference between the expected present value of the revenues, $E(R^{(n)})$, and the expected capitalized cost per approved biosimilar, $E(CC_j)$. The revenues are conditional on a pre-selected entry order n. Thus, the ENPV per approved biosimilar drug is:

$$ENPV = E(CC) - E\left(R^{(n)}\right) \tag{16}$$

In equation 17, the expected present value of lifetime revenues for a biosimilar manufacturer, $E(R^{(n)})$, is computed as the sum of the quarterly revenues over a 10-year period starting at $t = 0$ years and ending at $t = T = 9.75$ years:

$$E\left(R^{(n)}\right) = \sum_{t=0}^{T} \frac{R_t^{(n)}}{(1+r)^t} \tag{17}$$

In the preceding equation, r is the opportunity cost of capital (net of inflation), as before. As noted above, if the ENPV (equation 16) is positive, then this means the expected present value of revenues are greater than the expected present value of costs, making a biosimilar product a profitable endeavor overall.

Using a typical biosimilar development pathway, we calculate the contribution each stage of development makes to the total cost (Section 5.1) and the typical ENPV for various market sizes and market entry orders (Section 5.2). By performing the ENPV calculation under various development scenarios, we can assess the impact of barriers to biosimilar entry (Section 6.1), and the benefit of possible incentives (Section 6.2).

5 RESULTS

5.1 Cost Factor Analysis

Using our final ENPV model, we analyzed the impact of various factors on total costs of biosimilar development. In Table 24, we present the costs and durations of the biosimilar development stages for an average biosimilar entrant given the RP market size, measured in annual net sales. The total cost of development for an average biosimilar is about $135 million for RP markets greater than $1 billion, about $142 million for RP markets between $500 million and $1 billion, and about $131 million for markets less than $500 million. When we account for the cost of failed development programs, the average expected cost per approved biosimilar product is roughly $60 million higher for all RP market sizes.

Specific factors drive the total cost of biosimilar development more than others. For all RP market sizes, clinical studies account for most of the total cost of development. The CES stage of development makes up 41 to 42 percent of total costs depending on RP market size—more than any other stage of development. The next largest cost driver, for all RP market sizes, is the PK/PD similarity stage of development. PK/PD similarity development costs an average of $37 million for RP markets greater than $1 billion and also for RP markets less than $500 million. On average, the PK/PD similarity stage costs more, about $44 million, for markets that

are greater than $500 million but less than $1 billion. CMC is a substantial cost driver. The next highest cost driver, after the CES stage and the PK/PD similarity stage, is IP litigation, which is on average about 11 percent or 12 percent of the total development cost, depending on the market size. The preclinical stage of development increases in cost as the size of the market increases, and RP markets greater than $1 billion have the highest average cost of preclinical development at about $13 million. Following preclinical development, the launch preparation stage is the next highest cost driver at 8 percent of total costs for all market sizes. Lastly, biosimilar approval costs claim the smallest proportion of total development costs at about one percent for given RP markets of all sizes.

Table 24. Development Costs for an Average Biosimilar Entrant Given Various RP Market Sizes

Develop-ment Step	$1 Billion+			$500 Million–$1 Billion			$0–$500 Million		
	Average Cost (95% CI)	Percent of Total Cost	Duration in Months (95% CI)	Average Cost (95% CI)	Percent of Total Cost	Duration in Months (95% CI)	Average Cost (95% CI)	Percent of Total Cost	Duration in Months (95% CI)
Pre-Clinical Stage	$13,450,000 ($7,000,000, $14,050,000)	10%	39.5 (23.0, 41.0)	$12,461,364 ($7,000,000, $14,050,000)	9%	36.9 (23.0, 41.0)	$11,898,344 ($7,000,000, $14,050,000)	9%	35.5 (23.0, 41.0)
PK/PD similarity Stage	$37,079,678 ($19,856,040, $82,765,129)	27%	16.6 (11.9, 30.2)	$43,718,366 ($18,299,257, $94,334,747)	31%	17.7 (11.9, 30.2)	$37,399,232 ($18,299,257, $94,334,747)	29%	17.8 (11.9, 30.2)
CES Stage	$56,787,966 ($35,239,980, $81,350,573)	42%	31.7 (28.5, 40.9)	$58,006,226 ($31,836,630, $79,345,687)	41%	32.5 (28.5, 40.9)	$53,608,878 ($31,836,630, $79,345,687)	41%	32.5 (28.5, 40.9)
Subtotal: Clinical Studies (PK/PD similarity and CES Stages)	$93,867,645 ($55,096,020, $164,115,703)	69%	40.5 (32.4, 64.2)	$101,724,592 ($50,135,887, $173,680,434)	72%	42.5 (32.4, 64.2)	$91,008,110 ($50,135,887, $173,680,434)	69%	42.7 (32.4, 64.2)
Approval	$1,038,753 ($1,038,753, $1,038,753)	1%	24 (24.0, 24.0)	$1,038,753 ($1,038,753, $1,038,753)	1%	24 (24.0, 24.0)	$1,038,753 ($1,038,753, $1,038,753)	1%	24 (24.0, 24.0)
IP Litigation	$16,000,000 ($16,000,000, $16,000,000)	12%	23.6 (23.6, 23.6)	$16,000,000 ($16,000,000, $16,000,000)	11%	23.6 (23.6, 23.6)	$16,000,000 ($16,000,000, $16,000,000)	12%	23.6 (23.6, 23.6)
Launch Preparation Stage	$11,001,223 ($10,979,794, $11,467,294)	8%	23.6 (23.6, 23.6)	$11,013,885 ($10,979,794, $11,729,794)	8%	23.6 (23.6, 23.6)	$11,024,496 ($10,979,794, $11,729,794)	8%	23.6 (23.6, 23.6)
Total Cost	$135,357,620 ($90,114,567, $206,671,750)	n/a	n/a	$142,238,593 ($85,154,434, $216,498,981)	n/a	n/a	$130,969,704 ($85,154,434, $216,498,981)	n/a	n/a
Total Expected Cost	$199,244,571 ($118,270,000, $304,576,000)	n/a	n/a	$206,701,364 ($111,540,000, $302,730,000)	n/a	n/a	$188,665,364 ($111,540,000, $302,730,000)	n/a	n/a

Develop-ment Step	$1 Billion+			$500 Million–$1 Billion			$0–$500 Million		
	Average Cost (95% CI)	Percent of Total Cost	Duration in Months (95% CI)	Average Cost (95% CI)	Percent of Total Cost	Duration in Months (95% CI)	Average Cost (95% CI)	Percent of Total Cost	Duration in Months (95% CI)
Total Capitalized Cost	$212,180,857 ($130,500,000, $329,123,000)	n/a	n/a	$224,285,000 ($122,710,000, $328,830,000)	n/a	n/a	$205,826,291 ($122,710,000, $328,830,000)	n/a	n/a
Total Expected Capitalized Cost	$331,592,286 ($177,610,000, $507,959,000)	n/a	n/a	$344,297,727 ($167,010,000, $480,510,000)	n/a	n/a	$313,775,232 ($167,010,000, $480,510,000)	n/a	n/a

CI = confidence interval; n/a = not applicable

5.2 Expected Revenues and ENPV

We analyzed the expected lifetime revenues and ENPV for an average biosimilar entrant given our analytical model's baseline parameters and an RP market of greater than $1 billion, between $500 million and $1 billion, and less than $500 million. The results of this analysis are presented in Table 25. The total expected lifetime revenues, the discounted total expected lifetime revenues, and ENPV over the biosimilar's lifetime all decrease with entry order, regardless of market size. This indicates an advantage for early entrants. For example, the total expected lifetime revenue for the first entrant in an RP market greater than $1 billion is about $11 billion while the total expected lifetime revenue for the fourth or fifth entrant in the same size market is about $2 billion. Similarly, the ENPV for the first entrant in the same size market is about $9.5 billion while the ENPV for the fourth or fifth entrant is about $1.3 billion.

The highest total expected lifetime revenues and ENPVs are associated with the largest RP markets of greater than $1 billion, and the lowest total expected lifetime revenues and ENPVs are associated with the smallest RP markets of less than $500 million. For example, the total expected lifetime revenues are about $7 billion for a second entrant in an RP market greater than $1 billion and about $200 million for a second entrant in an RP market less than $500 million. Similarly, the ENPV for a second entrant in an RP market greater than $1 billion is about $6 billion, compared to -$131 million in an RP market less than $500 million in size. In fact, for all biosimilar entrants given a market of less than $500 million, the ENPV over the biosimilar's lifetime is negative, indicating biosimilar development in markets of that size may not be worth the investment. The same can be said of the fourth or fifth entrant in RP markets that are greater than $500 million and less than $1 billion. These findings agree with statements by experts that $500 million is the minimum RP market size for biosimilar development and markets between $500 million and $1 billion are only worthwhile if certain manufacturing or development efficiencies are available, e.g., because the company already markets other products in those same therapeutic areas [51].[33]

Table 25. Total Expected Lifetime Revenues and ENPV for an Average Biosimilar Entrant Given Various RP Market Sizes

Outcome Variable	Biosimilar Entry Order	$1 Billion+	$500 Million–$1 Billion	$0–$500 Million
		Baseline Amount (95% CI)	Baseline Amount (95% CI)	Baseline Amount (95% CI)
Total Expected Lifetime Revenues (Million $)	1	$10,847.8 ($3,127.5, $44,624.4)	$2,001.4 ($1,456.6, $2,622.5)	$309.5 ($0.7, $1,214.5)
	2	$7,157.2 ($2,063.5, $29,442.4)	$1,320.5 ($961.1, $1,730.3)	$204.2 ($0.5, $801.3)

[33] We did not have sufficient data to estimate the time between biosimilar product launches. This spacing varies considerably across markets and has decreased in recent years, with some products launching simultaneously. Because the model is based on older data, which likely overestimates the impact of earlier entry, we used the same launch date for all biosimilar products. This has a relatively small impact on results; if we instead apply a six-month lag between launches, then in a > $1 billion RP market, the ENPV would be 3.8 percent higher for the first entrant, 2.9 percent lower for the second entrant, 8.9 percent lower for the third entrant, and 14.9 percent lower for the fourth or fifth entrant. The main results represent a more realistic scenario for future biosimilars markets.

Outcome Variable	Biosimilar Entry Order	$1 Billion+ Baseline Amount (95% CI)	$500 Million–$1 Billion Baseline Amount (95% CI)	$0–$500 Million Baseline Amount (95% CI)
	3	$3,772.7 ($1,087.7, $15,519.9)	$696.1 ($506.6, $912.1)	$107.6 ($0.3, $422.4)
	4 or 5	$1,855.8 ($535.1, $7,634.3)	$342.4 ($249.2, $448.7)	$52.9 ($0.1, $207.8)
Total Expected Lifetime Revenues, Discounted (Million $)	1	$9,823.3 ($2,832.1, $40,410.1)	$1,812.4 ($1,319.1, $2,374.8)	$280.3 ($0.7, $1,099.8)
	2	$6,421.0 ($1,851.2, $26,414.1)	$1,184.7 ($862.2, $1,552.3)	$183.2 ($0.4, $718.9)
	3	$3,376.1 ($973.4, $13,888.2)	$622.9 ($453.3, $816.2)	$96.3 ($0.2, $378.0)
	4 or 5	$1,656.6 ($477.6, $6,814.7)	$305.6 ($222.4, $400.5)	$47.3 ($0.1, $185.5)
ENPV over Biosimilar Product's Lifetime (Million $)	1	$9,491.7 ($2,543.7, $40,002.8)	$1,468.1 ($868.0, $2,124.3)	-$33.5 (-$424.0, $762.2)
	2	$6,089.4 ($1,562.8, $26,006.8)	$840.4 ($411.1, $1,307.2)	-$130.6 (-$426.8, $412.7)
	3	$3,044.5 ($699.2, $13,480.9)	$278.6 ($2.3, $574.4)	-$217.5 (-$432.3, $63.6)
	4 or 5	$1,325.0 ($202.9, $6,407.4)	-$38.7 (-$228.6, $188.3)	-$266.5 (-$463.6, -$101.3)

CI = confidence interval; ENPV = expected net present value

6 ANALYSIS OF BARRIERS AND INCENTIVES TO MARKET ENTRY

6.1 Barriers

Several barriers to biosimilar market entry have been alluded to in previous sections: the cost, time, and complexity of analyzing the reference molecule and its CQAs; creating a biosimilar molecule that matches the RP; the much higher cost (compared to small molecule generics) of lengthy safety and efficacy studies with patient/subjects to confirm what analytics, in vitro studies, and PK/PD studies had already established with greater precision; the probability of a patent dispute with the RP company that could delay market entry for years after CDER approval. There are other barriers summarized below.

Rebates and reimbursement. As was frequently the case with brand drugs, RP manufacturers, with few exceptions, offer substantial percentage rebates off their list prices for retail drugs. Rebates can lower the actual net price paid to the manufacturer substantially and the terms are secret, so biosimilars entering the market often do not know the price point with which they are competing.

- *Private health plans*. A 2020 study of biosimilar coverage decisions by 17 of the largest commercial health plans in the United States found that just 14 percent of decisions favored the biosimilar while 33 percent favored the RP [76]. The authors

suggested that undisclosed rebates to the plans could be the reason for the disparity. Ten of the 17 plans never preferred the biosimilar.

- *Medicare reimbursement*. Medicare now reimburses providers based on the average wholesale price of the medication + 6 percent (for RPs) and + 8 percent for biosimilars in the case of Medicare Part B. Providers, however, often receive rebates from RP manufacturers in the case of physician-administered drugs—a point made by multiple experts [51]. Providers may still be incentivized to prescribe the higher-priced alternative if 6 percent of the higher-priced RP exceeds 8 percent of a lower-priced biosimilar, or if rebates paid by the manufacturer to the provider make up the difference in the CMS reimbursement.

Provider and patient buy-in. For the first few years after biosimilars were introduced on the market, there was hesitation and wariness from physicians to prescribe them. Unlike small molecule generic drugs, biosimilars are not automatically substitutable with their RPs—unless they have received interchangeable designation from FDA—even though they have "no clinically meaningful differences in safety, purity or potency (safety and effectiveness) compared to the reference product," in accordance with FDA standards [4]. This coupled with lack of detailed knowledge regarding the highly precise analytical studies, comparison studies, PK/PD studies, and intense post-approval quality control measures that biosimilars go through to ensure that they will replicate the clinical effects of the RP appears to have led to confusion among providers. In a survey of over 500 physicians across several specialty fields that was fielded in December 2019, Kolbe et al. [77] found that, "Fewer than half had a baseline understanding of key elements of biosimilarity, even among respondents who had previously prescribed a biosimilar."

Physician surveys have shown that biosimilars gained more acceptance among treating physicians, both in the United States and in Europe, over time. In the EU countries where biosimilars have been available the longest, such as Holland, acceptance and use is highest. A survey of 268 U.S. oncologists in 2021 revealed that 236 (88 percent) treated patients with biosimilars and 63 percent were required to do so by hospital policies [78].

In a recent report of a 2022 physician's workshop on biosimilars in the United States co-sponsored by FDA [79], the primary barriers identified by participants were (1) lack of availability of biosimilars, mainly due to market entry being stifled by originators' patents and court filings; (2) prescribers' unfamiliarity with the biosimilar development paradigm and FDA's approval standards; (3) concern about potential immunogenicity impacts on patients; (4) administrative burden associated with biosimilar prescribing, plus modest patient savings, which combine to disincentivize prescribing them. Some specialists were also focused on specific concerns. Oncologists feared product variability and "drift;" gastroenterologists were concerned about lack of patient awareness and getting a nocebo effect in too many patients if they switched them to biosimilars [79].

There is no question that uptake has been increasing over the past few years, but it is noticeably uneven across specialties. It is also possible that uptake may reach an asymptote at a level of use lower than that achieved by generic drugs. Several aspects inherent to the biologic marketplace undercut the natural advantage of a lower-priced, well-regulated product that is of

equal quality, carefully manufactured, and scientifically proven to be effective at a microscopic level. If a serious illness is being successfully treated or avoided with a biologic, switching the patient to a biosimilar could seem a pointless risk to many doctors and patients. Hence, the severity and intractability of many diseases treated by biologics can have been inhibiting uptake surely makes switching to a biosimilar during a successful course of treatment seem riskier to patients and physicians. The complexity of the biologic molecule and its mechanism of action are more challenging for patients to grasp than explanations of a small molecule generic, which simply uses the same active ingredient as the brand drug.

Lack of Transparency. BPCIA created a well-intentioned procedure, the patent dance, for rival companies to exchange information so that each of them could gauge their mutual strengths and weaknesses and hopefully avoid engaging in protracted patent litigation. The exchange of patent information during this process, it was thought, made it unnecessary to mandate listing all patents in the Purple Book, as is the case with small molecule brand drugs in the Orange Book. However, in Sandoz v. Amgen, 137 S.Ct. 1664 (2017), the Supreme Court voted 9-0 to make participation in the patent dance optional. Legal observers have suggested that applying the patent rules of the Orange Book to the Purple Book would limit the number of patents by the RP and protect confidential business information—such as the details of the biosimilar's manufacturing process—from being exposed.

The continued secrecy surrounding rebates and other contract terms offered by brand drug and RP manufacturers to pharmacy benefit managers (PBMs) also makes market entry more problematic and inhibits uptake of biosimilars, as described above. Legislation promoting transparency of rebate amounts, who benefits from them, and pricing information has been attempted in Congress and some state legislatures, but the "safe harbor" where this information has been lying for years remains generally undisturbed. At the federal level, HHS "Rebate Rule" sought to eliminate safe harbor protections for manufacturer rebates to PBMs, thereby encouraging the use of discounts that directly benefit patients at the point of sale rather than being retained by PBMs or health plans [80]. Even though the rule was finalized in 2020, its implementation has been pushed to January 1, 2026, due to a court-ordered delay [81]. In Congress, bills such as the "Creating Transparency to Have Drug Rebates Unlocked (C-THRU) Act OF 2019" were introduced that would require PBMs to disclose rebate and discount information, empowering plan sponsors and patients to see how much of these negotiated savings translate into lower premiums or reduced out-of-pocket spending [82]. However, the fate of these bills remain uncertain. At the state level, numerous laws mandate advance notification of planned price increases, reporting of manufacturer costs, and disclosure of PBM-negotiated rebates [83]. For instance, Texas' SB 1296 compels PBMs to disclose rebate agreements with drug manufacturers and how those rebates are allocated or passed on to the plan sponsor [84]. Table 26 provides an overview of different current initiatives at the federal level.

Table 26. Recently Introduced PBM-related Federal Legislation in the 118th Congress

Name of Bill	Bill ID, Introduction Date	Sponsor(s)	Latest Action
S. 127 Pharmacy Benefit Manager Transparency Act of 2023	**S.127 118th Congress 01/26/2023,**	**Sen. Cantwell [D-WA]**	**12/13/2023 Placed on Senate Legislative Calendar under General Order**
Prohibits PBMs from arbitrarily, unfairly, or deceptively (1) clawing back reimbursement payments, or (2) increasing fees or lowering reimbursements to pharmacies to offset changes to federally funded health plans			
S. 1339 Pharmacy Benefit Manager Reform Act	**S. 1339 118th Congress 04/27/2023**	**Sen. Sanders [I-VT]**	**06/22/2023 Placed on Senate Legislative Calendar under General Orders. Calendar No. 113.**
▪ Prohibits spread pricing. ▪ Requires an exception process for patients undergoing a medication step therapy protocol. ▪ Limits revenue sources for PBMs, requiring additional data disclosure by health plans, and restricting contracting terms. ▪ PBMs must remit to the [client] all rebates, fees, alternative discounts, and other remuneration received from a drug manufacturer. ▪ PBMs must report to plan sponsors various details of deals with manufacturers.			
S. 2973 - Modernizing and Ensuring PBM Accountability Act	**S. 2973 118th Congress 09/28/2023**	**Sen. Wyden [D-OR]**	**12/07/2023 Placed on Senate Legislative Calendar under General Orders. Calendar No. 266.**
▪ Enhances transparency into PBM-insurer operations ▪ Improves patient access to community pharmacies. ▪ Ensures fair pharmacy reimbursements based on actual acquisition and dispensing costs.			
H.R.5372 - Expanding Seniors' Access to Lower Cost Medicines Act of 2023	**H.R.5372 118th Congress 09/08/2023)**	**Rep. Joyce, John [R-PA-13]**	**12/06/2023 Ordered to be Reported (Amended) by the Yeas and Nays: 48-0**
Allows Part D plans to add biosimilar biological products to their formularies and change the cost-sharing status of a reference biological product after the first 60 days of a plan year.			
H.R.5385 Medicare PBM Accountability Act	**H.R.5385 118th Congress 09/12/2023**	**Rep. Landsman, Greg [D-OH-1]**	**12/17/2024 Referred to the Subcommittee on Health.**
▪ Requires PBMs to provide plan sponsors with information about PBM-affiliated entities and contractors, rationales for formulary decisions, and explanations for benefit designs that favor certain pharmacies. ▪ Allows Part D plans to audit PBMs.			
H.R.7535 Prescription Drug Supply Chain Pricing Transparency Act	**H.R.7535 118th Congress 03/05/2024**	**Rep. Caraveo, Yadira [D-CO-8]**	**12/17/2024 Referred to the Subcommittee on Health**
Requires the Comptroller General of the United States to conduct a study on the use of compensation and payment structures related to a prescription drug's price within the retail prescription drug supply chain. Such study shall include ▪ An overview of the type, magnitude, other features (such as the pricing benchmarks used), and prevalence of compensation and payment structures related to a prescription drug's price, such as calculating fee amounts as a percentage of a prescription drug's price, between intermediaries in the prescription drug supply chain. ▪ Primary business models and compensation structures for each category of intermediary. ▪ Variation in price-related compensation structures between affiliated entities (such as entities with common ownership, either full or partial, and subsidiary relationships) and unaffiliated entities.			
H.R.7717 To amend title XI of the Social Security Act to enhance pharmacy benefit manager transparency requirements.	**H.R.7717 118th Congress 3/19/2024**	**Sen. Ruben Gallego [D-AZ]**	**3/22/2024 House Referred to the Subcommittee on Health.**

Name of Bill	Bill ID, Introduction Date	Sponsor(s)	Latest Action
Enhances pharmacy benefit manager transparency requirements by applying transparency-related reporting requirements to PBM and their affiliates under a contract with (i) a prescription drug plan sponsor or a Medicare Advantage organization offering a Part D plan or (ii) a qualified health benefits plan. Such reports would be publicly available on the Centers for Medicare and Medicaid Services website and would include the amount of utilization-related fees the PBM receives from manufacturers, as well as the amount and percentage of fees passed through to the plan sponsor or issuer.			
H.R, 6283 **The Delinking Revenue From Unfair Gouging (DRUG) Act**	**H.R, 6283** **118th Congress** **3/19/2024**	**Sen. Ruben Gallego [D-AZ]**	**3/22/2024 House Referred to the Subcommittee on Health.**
▪ Requires, with respect to the Federal Employee Health Benefits program (FEHBP), that PBM's service fees be set at a flat dollar amount and ▪ Prohibits PBMs from charging fees based on (i) drug prices or benchmark prices (such as wholesale acquisition cost or average wholesale price) and (ii) discounts, rebates, fees, or other direct or indirect remuneration. ▪ Prohibits PBMs from steering patients to affiliated pharmacies.			
H.R, 8261 **The Preserving Telehealth, Hospital, and Ambulance Act**	**H.R, 8261** **118th Congress** **05/07/2024**	**Rep. Schweikert, David [R-AZ-1]**	**House - 12/19/2024 Placed on the Union Calendar, Calendar No. 786**
For PBMs contracting with a Part D prescription drug plan: ▪ Prohibits PBMs from receiving remuneration for services other than bona fide service fees (incentive payments and rebates passed through to the plan sponsor do not violate this requirement). ▪ Beginning in 2027, requires PBMs to submit a yearly report to the plan sponsor and the secretary of Health and Human Services providing information on the drugs provided under the plan and any affiliate arrangements related to the dispensing of drugs, among other information. ▪ Requires PBMs to provide plan sponsors with a written explanation of agreements with drug manufacturers. ▪ Establishes audit rights for plan sponsors. ▪ Calls for the comptroller general of the United States and the Medicare Payment Advisory Committee to submit a report to Congress regarding prescription drug cost transparency and agreements with PBMs, respectively.			

Sources: Adapted from Faegre Drinker (2024) [85]

6.1.1 Hurdles to Interchangeability

According to BPCIA, "a biologic is interchangeable if it meets the biosimilarity requirements and fulfills two additional criteria" 42 USC §262(k)(4). First, there is a clinical efficacy hurdle to clear: the biologic must "be expected to produce the same clinical result as the reference product in any given patient" 42 USC §262(k)(4)(A)(ii). Second, it must be safe for a patient to switch between the RP and the follow-on biologic 42 USC §262(k)(4)(B). In particular, if the biologic is a product that is administered more than once to an individual, "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch" 42 USC §262(K)(4)(B).

6.1.1.1 Historical Perspective on Interchangeability

Interchangeability was evidently written into BPCIA as an incentive, following the successful market penetration of generic small molecule drugs enabled by the 1984 Hatch-Waxman amendments to the Public Health Service Act. Hatch-Waxman provided an

abbreviated approval process for chemical generics, as well as six months of exclusive presence in the market for the first generic applicant that successfully overcame the brand drug's patents. As generics gained footholds in numerous markets, insurers, including virtually all state programs, began to mandate that pharmacies substitute a generic drug, if available, when presented a prescription for a brand drug (unless the prescriber of a brand drug indicated "dispense as written" (DAW) on the prescription).

BPCIA emulated the major elements of Hatch-Waxman that had propelled generic competition in small molecule drug markets but modified them in recognition of the much greater complexity of biologic molecules in structure, mechanism of action, method of production, transport, and storage.[34] The additional requirements for a biosimilar to be designated as "interchangeable"—and thus qualify for automatic substitution for the RP at the pharmacy—had no counterpart in Hatch-Waxman. A generic small molecule drug approved by FDA is considered the same as the brand drug and all 50 states allow pharmacies to dispense a generic to fill prescriptions written for a brand drug without consulting the prescriber (unless the prescriber specifies that only the brand drug be dispensed).

The term "biosimilar" itself accurately reflects the complexities of biologics' molecular structures and production methods; and was meant to avoid leading patients or physicians into the belief that an RP and a biosimilar are "the same." However, the term has not encouraged biosimilar uptake in the same way that the term "bioequivalent" has done for generic small molecule drugs.

The additional designation of interchangeability suggests that there are two tiers of biosimilars, and that an interchangeable is closer to the RP, if not safer and more efficacious, than a biosimilar that has not undergone the additional clinical testing—i.e., a switching study—that interchangeable designation apparently required. Even before the first FDA approval of a biosimilar in March 2015, the two tiers of biosimilars were seen by analysts to pose an important challenge to biosimilar uptake. "The key to expediting a shift to biosimilars is to establish interchangeability" [86].

Per BPCIA, a biosimilar must demonstrate that there are "no clinically meaningful differences between the biological product and the RP in terms of the safety, purity, and potency of the product" 42 USC §262(i)(2)(B). Interchangeable designation is for applicants that fulfill the requirements for biosimilarity and also have demonstrated that they can "be expected to produce the same clinical result as the reference product in any given patient..." and "... It must be safe for a patient to switch between the reference product and the follow-on biologic..." Further, for biologics normally administered more than once, the interchangeable candidate must show that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than

[34] A generic drug's abbreviated new drug application (ANDA) will not be approved by FDA until at least five years have passed since the reference brand drug was approved; biosimilars must wait four years after the RP's approval before FDA will accept their abbreviated BLA, and another eight years before FDA will approve it. This provides the RP at least 12 years in the market without biosimilar competition. The first-to-file generic drug in a market can qualify for 6 months of exclusive presence in the market, whereas the first interchangeable biosimilar in a market can be the only interchangeable in its market for 12 months.

the risk of using the reference product without such alternation or switch" 42 USC §262(k)(4)(B). Despite FDA's repeated assurances and educational efforts, the idea that there are two tiers of biosimilars has been difficult for physicians to shake off.

Referring to FDA's initial guidance for industry regarding interchangeability,[35] one author asserted, "This document alone shows that interchangeability will not be utilized by most biosimilar manufacturers. The studies and analyses would likely be unduly burdensome and costly, intensifying the delayed emergence of biosimilars" [87] [author's footnotes omitted].

Even before Kobalia [87] predicted minimal interest among manufacturers in pursuing interchangeable designation, there was evidence of the role such designation might play in biosimilar uptake. Cohen et al. [88] performed a survey of 1,200 U.S. physicians in six specialties that often use biologics from November 2015 to January 2016. The authors reported that 55 percent of specialists disagreed that "biosimilars will be safe and appropriate for use in naïve and existing patients." Fifty-three percent agreed that "it would be essential for doctors to have data directly evaluating the safety of switching patients from an originator biologic to its biosimilar" [88].[36]

Subsequent analysts of biosimilar uptake in the United States elicited the attitudes and opinions of prescribers and payers through surveys or focus groups. They also found that physicians' confidence in the safety and efficacy of a biosimilar would be augmented by study results that would support the interchangeable designation. For instance, in their survey of 300 managed care and specialty pharmacy professionals, Greene et al. [89] found that "...the strategy with the highest pooled likelihood rating (91 percent) was educational programs for prescribers focusing on evidence from studies in which patients switched from RPs to biosimilars."[37]

BPCIA recognized the importance of pharmacy substitution in advancing the ubiquitous acceptance of generic drugs by providing for the interchangeable designation. However, in the first years of biosimilar development, as Kobalia predicted, manufacturers were evidently not often tempted to bear the extra expense and delay that clinical switching studies would incur.[38] The extent to which lack of interchangeable designation contributed to the initially disappointing uptake of biosimilars that were approved and launched from 2015 to 2020 is

[35] Kobalia [86] was referring to a draft guidance, U.S. FDA, [137] *Considerations in Determining Interchangeability with a Reference Product: Guidance for Industry*. The final guidance, with few changes from the 2017 draft [151], was issued May 10, 2019.

[36] Regarding the importance of data about switching between an RP and a biosimilar, the authors pointed out that "as of September 2016, all biosimilar products approved by the FDA have incorporated at least one switch from originator biologic to biosimilar into their biosimilar clinical development programs" [87].

[37] Greene et al. [88] asked respondents to rate strategies as extremely likely; likely; uncertain; unlikely; or extremely unlikely "to overcome barriers to adopting biosimilars and achieving BPCIA's goals." Fifty-four percent of respondents rated "clear FDA guidance on substitution" as an extremely likely strategy (an additional 36 percent rated it as likely); 39 percent rated "prescriber education on switching studies" as extremely likely (52 percent rated it as likely).

[38] Switching studies in this context are clinical trials in which some patients are switched back and forth between the RP and the biosimilar to ensure that switching to a biosimilar—and switching back again—is clinically the same as continuing treatment with the RP.

difficult to pinpoint. For instance, the first interchangeable, Semglee (insulin glargine-yfgn), has had limited market share despite its interchangeable status. Possible reasons are (1) Semglee's WAC, $269, was too close to that of the RP, Lantus, at $292; (2) Viatris also marketed an unbranded version of Semglee with a WAC of $99, which was also interchangeable with Lantus; and (3) lack of payer coverage in non-commercial channels (Medicare, Medicaid FFS, Managed Medicaid) [90].

6.1.1.2 Shift in Labeling for Biosimilars, 2018 to 2023

The changes in FDA's guidance for labeling biosimilars are representative of FDA's efforts to strengthen identification of biosimilars as being clinically equivalent to interchangeables and RPs. In October 2023, the FDA's director of the Office of New Drugs' Office of Therapeutic Biologics and Biosimilars, Dr. Sarah Yim, issued FDA's perspective on the draft guidance for industry "Labeling for Biosimilar and Interchangeable Biosimilar Products" (dated July 2023). "We believe that statements in the Prescribing Information identifying that products have been approved as interchangeable with the RP and describing the interchangeability standard are not necessary for informing the safe and effective use of the product to prescribing health care professionals" [17]. The 2023 draft guidance on labeling was open for public comment until November 2023. Of the nine comments received, eight supported FDA's recommendation as a step to inhibit the incorrect inference that interchangeable biosimilars were likely to be safer or more efficacious than biosimilars that were not so designated.

Table 27 summarizes milestones in the development of each of the 17 interchangeables approved by FDA through August, 2024. As can be seen, the intervals between a biosimilar's approval and its approval as an interchangeable have recently been diminishing. Indeed, several have apparently applied for interchangeable and biosimilar status simultaneously. The first biologic product to gain interchangeable designation was Semglee (insulin glargine-yfgn), in July 2021. Semglee had already been approved by FDA via a 505(b)(2) New Drug Application (NDA) in June 2020. Eleven of the 17 currently approved interchangeables have been approved since October 2023, and, owing to ongoing patent litigation or settlement agreements, just seven interchangeables have launched commercially in the U.S. market. As of September 1, 2024, the median time in the market for these seven interchangeables is 14 months.

The most probable reasons for the acceleration of interchangeable approvals are (1) the perception by biosimilar sponsors that interchangeable designation, despite the additional cost and/or delay in reaching the market, will provide an advantage in volume and dollar sales over biosimilar competitors; (2) the possibility of being the only interchangeable in the market for a year, an exclusivity provided for in BPCIA to the first interchangeable to enter a market; and (3) the perception among biosimilar applicants that FDA is increasingly amenable to using results from robust in vitro analyses, bioassays, PK/PD similarity PK studies, to provide evidence that the biosimilar applicant qualifies for interchangeable status as defined by BPCIA.

As can be inferred from Table 28, FDA seems prepared to be less insistent on a switching study for some interchangeable candidates, particularly less complex molecules (such as insulin glargine) and biosimilars that are not injected directly into the bloodstream, such as the interchangeables for Eylea and Lucentis.

Table 27. Seventeen Approved Interchangeables [c] for the U.S. Market and their Seven Reference Products through August 20, 2024

RP: Proprietary name (proper name) (Company)	RP Approval Date	Interchangeable Proprietary Name	Interchangeable Proper Name	Interchangeable Manufacturer	Biosimilar Approval Date	Interchangeable Approval Date	Months from Biosimilar approval to Interchangeable designation	Interchangeable U.S. launch date *proposed launch date italicized*	Months in U.S. Market to September 1, 2024
Humira (adalimumab) (AbbVie)	12/31/2002	Abrilada	adalimumab-afzb	Pfizer	11/15/2019	10/5/2023	47.3	11/20/2023	9.3
		Cyltezo	adalimumab-adbm	Boehringer Ingelheim	8/25/2017	10/14/2021	50.4	7/1/2023	14
		Simlandi	adalimumab-ryvk	Alvotech/Teva, Quailent	2/24/2024	2/24/2024	0.0	5/21/2024	3.3
		Hyrimoz	adalimumab-adaz	Sandoz	10/31/2018	5/8/2024	67.3	5/8/2024	3.7
		Hadlima	adalimumab-bwwd	Samsung Bioepis	7/23/2019	6/28/2024	59.2	6/28/2024	1.5
		Amjevita	adalimumab -atto	Amgen	9/23/2016	8/20/2024	94.9	8/20/2024	0.3
Prolia/Xgeva (denosumab) (Amgen)	6/1/2010	Jubbonti/Wyost	denosumab-bbdz	Sandoz-Hexal	3/5/2024	3/5/2024	0.0	*5/31/2025 [b]*	Not yet launched
Lantus (insulin glargine) (Sanofi Avantis)	4/20/2000	Rezvoglar	insulin glargine-aglr	Eli Lilly	12/17/2021	11/16/2022	11.1	4/1/2023	17
		Semglee [a]	insulin glargine-yfgn	Biocon Biologic	6/11/2020 [a]	7/28/2021	13.5	11/16/2021	33.5
Lucentis (ranibizumab) (Genentech)	6/30/2006	Byooviz	ranibizumab-nuna	Samsung	9/17/2021	10/3/2023	24.9	10/3/2023 [c]	11
		Cimerli	ranibizumab-eqrn	Coherus BioSciences	8/2/2022	8/2/2022	0.0	10/3/2022	20.1
Stelara (ustekinumab) (Janssen Biotech)	9/25/2009	Wezlana	ustekinumab-auub	Amgen	10/31/2023	10/31/2023	0.0	*1/1/2025*	Not yet launched
		Pyzchiva	ustekinumab-ttwe	Samsung Bioepis	6/28/2024	Provisional [d]	TBD	*2/22/2025 [e]*	Not yet launched
Eylea (aflibercept) (Regeneron)	11/25/2011	Yesafili	aflibercept-jbvf	Biocon Biologic	5/20/2024	5/20/2024	0.0	in litigation	Not yet launched
		Opuviz	aflibercept-yszy	Samsung Bioepis	5/20/2024	5/20/2024	0.0	in litigation	Not yet launched
		Enzeevu	aflibercept -abzv	Sandoz	8/9/2024	Provisional [d]	0.0	in litigation	Not yet launched
Soliris (eculizumab) (Alexion)	3/16/2007	Bkemv	eculizumab-aeeb	Amgen	5/28/2024	5/28/2024	0.0	*3/1/2025*	Not yet launched

RP = reference product; TBD = to be determined

[a] Semglee was approved for treatment of diabetes via a 505(b)(2) New Drug Application (NDA) on 6/11/2020. It was designated as an interchangeable biosimilar on 7/28/2021.

[b] Settlement called for U.S. launch of Jubbonti/Wyost to be "May 31, 2025, or earlier under certain circumstances if customary acceleration provisions are triggered" [91].

[c] Byooviz launched as a biosimilar on 6/1/2022; as it was already in the market when it was approved as an interchangeable on 10/3/2023, we use that date as its interchangeable launch date.

[d] "...the FDA provisionally determined that [this biosimilar] would be interchangeable with the reference medicine as it is currently subject to an unexpired period of exclusivity for the first interchangeable biosimilar biological products" [92].

[e] The launch date for Pyzchiva was agreed to by Janssen during settlement negotiations.

Table 28. Characteristics of Switching Studies Performed to Gain Interchangeable Designation

RP: Proprietary name (proper name) (Company)	Interchangeable Proprietary Name	Proper Name	Switching Study ID, CT.GOV	Switching Arm Sample Size, CT.GOV	Study Duration	Study Start	Study Completion	Study Duration, Months
Humira (adalimumab) (AbbVie)	Yuflyma [a]	adalimumab-aaty	NCT05495568	366	52 weeks	11/7/2022	2/1/2024	14.9
	Cyltezo	adalimumab-adbm	NCT03210259	259	58 weeks	7/10/2017	4/16/2019	21.3
	Abrilada	adalimumab-afzb	NCT04230213	455	62 weeks	1/13/2020	6/22/2021	17.3
	Simlandi	adalimumab-ryvk	NCT04453137	567	48 weeks	6/30/2020	11/16/2021	16.6
	Hyrimoz	adalimumab-adaz	NCT04422171	400	52 weeks	6/19/2020	1/31/2023	30.3
	Hadlima	adalimumab-bwwd						
	Amjevita	adalimumab -atto						
Prolia/Xgeva (denosumab) (Amgen)	Jubbonti/Wyost	denosumab-bbdz	NCT03974100	124	26 weeks	7/2/2019	4/22/2022	33.8
Lantus (insulin glargine) (Sanofi Avantis)	Semglee	insulin glargine-yfgn	NCT02666430	127	36 weeks	Dec-15	Jul-17	19.1
	Rezvoglar	insulin glargine-aglr	[b]	n/a	n/a	n/a	n/a	n/a
Lucentis (ranibizumab) (Genentech)	Byooviz	ranibizumab-nuna	[c]	n/a	n/a	n/a	n/a	n/a
	Cimerli	ranibizumab-eqrn	[c]	n/a	n/a	n/a	n/a	n/a
Stelara (ustekinumab) (Janssen Biotech)	Wezlana	ustekinumab-auub	[d]	n/a	n/a	n/a	n/a	n/a
	Pyzchiva	ustekinumab-ttwe	Provisional [d][e]	[e]	[e]	[e]	[e]	[e]
Eylea (aflibercept) (Regeneron)	Yesafili	aflibercept-jbvf	[c]	n/a	n/a	n/a	n/a	n/a
	Opuviz	aflibercept-yszy	[c]	n/a	n/a	n/a	n/a	n/a
	Enzeevu	aflibercept-abzv	Provisional [c][f]	n/a	n/a	n/a	n/a	n/a
Soliris (eculizumab) (Alexion)	Bkemv	eculizumab-aeeb	NCT03818607 [g]	42 [g]	26 weeks	1/22/2019	7/12/2022	41.8

RP = reference product; n/a = not applicable

[a] Yuflyma was approved as a biosimilar in May 2023; Celltrion expects to gain interchangeable status by the end of the year 2024.

[b] FDA required no additional clinical data for interchangeable designation.

[c] FDA required no additional clinical data for interchangeable designation. Per CDER, switching studies are not needed for eye injectables because potential for immunogenicity is so low [93].

[d] FDA required no additional clinical data for interchangeable designation of Wezlana. "FDA determined late in the review that switching studies generally would not be needed for interchangeable ustekinumab products, prompting Amgen to seek the designation" [94].

[e] Media reports stated that Pyzchiva's interchangeability designation was provisional due to issues of exclusivity around previously approved interchangeables. One CES is recorded for SB17 (Pyzchiva) in clinicaltrials.gov, but the report did not make clear whether the protocol qualified as a switching study. See https://clinicaltrials.gov/study/NCT04967508?term=SB17&rank=1#study-plan.

[f] Media reports stated that Enzeevu's interchangeability designation was provisional due to issues of exclusivity around previously approved interchangeables. See, for instance, Truong [95] at https://piemagazine.org/sandozs-anti-vegf-biosimilar-secures-fda-approval-for-namd-treatment/.

[g] The small number of patient subjects in Bkemv's CES is likely due to the rare disease status of the conditions treated by eculizumab. A 26-week switching arm was added to a 52-week CES. Eculizumab is approved in the United States to treat paroxysmal nocturnal hemoglobinuria (PNH), to reduce hemolysis, atypical hemolytic uremic syndrome, to inhibit complement-mediated thrombotic microangiopathy, and to treat neuromyelitis optica spectrum disorder.

6.1.1.3 Impact of Removing Interchangeability Hurdle

Given the number of interchangeables launched in the U.S. market and the duration of their market experience, there are insufficient data to draw generalizable conclusions about the impact of interchangeable status on their market uptake. Thus, whether the interchangeable designation actually confers an advantage in volume and dollar sales over biosimilar competitors in the U.S. market cannot yet be measured. However, using the analytical model developed, it is possible to examine the impact of the recent changes in FDA's approach toward accepting evidence from in vitro analyses, bioassays, PK/PD similarity studies in lieu of switching studies for a biosimilar applicant to qualify for interchangeability designation.

Table 29, Table 30, and Table 31 present the results of this analysis (separated by market size) when we evaluated the impact of removing the requirement for a switching study to gain interchangeability designation under the BPCIA for each of the 256 RPs that currently do not have competing biosimilars in the U.S. market. Our results show that for biosimilar markets greater than $1 billion, the elimination of the need to conduct switching studies reduces the average total cost of development by $14.1 million (9 percent) from $149.5 million down to $135.4 million and lowers the average development time by 1.1 years (9 percent) from 11.7 years down to 10.6 years. When failure and capital costs are included, the reduction in the average expected capitalized cost of development is $54.2 million (14 percent). Similar effects on development duration and average total costs for the same scenario were observed when we ran the model for biosimilars with markets less than $500 million and those with markets between $500 million and $1 billion.

For biosimilar markets of all sizes, removing the requirement for a switching study also increases the expected ENPV of the biosimilar over its lifetime. For example, for markets greater than $1 billion, the expected ENPV for the first entrant increases by $54.2 million (one percent) and the expected ENPV for the fourth or fifth entrant increases by $54.2 million (15 percent). For markets between $500 million and $1 billion, the expected ENPV increases by $60.5 million regardless of entry order and for markets less than $500 million the expected ENPV increases by $55.8 million regardless of entry order.

Table 29. Estimated Impact on Biosimilars of Removing the Interchangeability Hurdle given an RP Market of Less Than $500 Million per Year Prior to Biosimilar Entry

Parameters	
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)
Location of PK/PD similarity Study	40% US and 60% EU
Bridging Study Needed?	Yes
CES Needed?	Yes
Location of CES	40% US and 60% EU
Switching Study Needed?	Depends on scenario
Device Development Needed?	No

Parameters				
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline Switching Study	Change Scenario No Switching Study	Difference
Total Cost ($ Million)	All	$145.87 ($96.0, $240.2)	$130.97 ($85.2, $212.3)	-10.2% (-12.2%, -8.0%)
Total Expected Cost ($ Million)		$207.42 ($125.2, $337.8)	$188.67 ($111.5, $302.7)	-9.1% (-11.7%, -6.8%)
Total Capitalized Cost ($ Million)		$244.79 ($145.2, $391.5)	$205.83 ($122.7, $328.8)	-15.5% (-19.6%, -12.2%)
Total Expected Capitalized Cost ($ Million)		$369.62 ($196.9, $565.0)	$313.78 ($167.0, $480.5)	-14.7% (-18.9%, -11.4%)
Total Expected Drug Development Duration (Years)		11.6 (9.5, 14.4)	10.5 (8.6, 12.7)	-9.8% (-12.4%, -8.2%)
Total Expected Lifetime Revenues (Million $)	1	$309.49 ($0.7, $1,214.5)		No Change
	2	$204.20 ($0.5, $801.3)		
	3	$107.64 ($0.3, $422.4)		
	4 or 5	$52.95 ($0.1, $207.8)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$280.26 ($0.7, $1,099.8)		No Change
	2	$183.19 ($0.4, $718.9)		
	3	$96.32 ($0.2, $378.0)		
	4 or 5	$47.26 ($0.1, $185.5)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	-$89.35 (-$514.4, $728.5)	-$33.51 (-$424.0, $762.2)	47.4% (5.5%, 340.6%)
	2	-$186.42 (-$515.7, $337.2)	-$130.58 (-$426.8, $412.7)	49.6% (10.9%, 277.0%)
	3	-$273.29 (-$521.3, $24.4)	-$217.45 (-$432.3, $63.6)	79.4% (11.5%, 248.8%)
	4 or 5	-$322.35 (-$551.7, -$138.5)	-$266.51 (-$463.6, -$101.3)	18.9% (11.5%, 29.3%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 30. Estimated Impact on a Biosimilar of Removing Interchangeability Hurdle given an RP Market Greater Than $500 Million but Less Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Yes			
Location of CES	40% US and 60% EU			
Switching Study Needed?	Depends on scenario			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline Switching Study	Change Scenario No Switching Study	Difference
Total Cost ($ Million)	All	$158.40 ($96.0, $240.2)	$142.24 ($85.2, $212.3)	-10.1% (-12.2%, -8.0%)
Total Expected Cost ($ Million)		$227.05 ($125.2, $337.8)	$206.70 ($111.5, $302.7)	-8.9% (-11.1%, -6.8%)
Total Capitalized Cost ($ Million)		$266.43 ($145.2, $391.5)	$224.29 ($122.7, $328.8)	-15.4% (-19.6%, -12.2%)
Total Expected Capitalized Cost ($ Million)		$404.77 ($196.9, $565.0)	$344.30 ($167.0, $480.5)	-14.6% (-18.9%, -11.4%)
Total Expected Drug Development Duration (Years)		11.7 (9.5, 14.4)	10.6 (8.6, 12.7)	-9.6% (-12.4%, -8.2%)
Total Expected Lifetime Revenues (Million $)	1	$2,001.37 ($1,456.6, $2,622.5)		No Change
	2	$1,320.47 ($961.1, $1,730.3)		
	3	$696.05 ($506.6, $912.1)		
	4 or 5	$342.39 ($249.2, $448.7)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$1,812.36 ($1,319.1, $2,374.8)		No Change
	2	$1,184.65 ($862.2, $1,552.3)		
	3	$622.87 ($453.3, $816.2)		
	4 or 5	$305.63		

Results				
			($222.4, $400.5)	
ENPV over Biosimilar Product's Lifetime (Million $)	1	$1,407.59 ($780.4, $2,088.5)	$1,468.07 ($868.0, $2,124.3)	5.0% (1.6%, 11.2%)
	2	$779.88 ($323.5, $1,271.4)	$840.36 ($411.1, $1,307.2)	10.2% (2.5%, 27.2%)
	3	$218.10 (-$85.4, $538.0)	$278.58 ($2.3, $574.4)	79.5% (5.7%, 416.8%)
	4 or 5	-$99.14 (-$316.3, $158.4)	-$38.66 (-$228.6, $188.3)	74.2% (19.0%, 241.3%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 31. Estimated Impact on Biosimilars of Removing Interchangeability Hurdle given an RP Market Greater Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Yes			
Location of CES	40% US and 60% EU			
Switching Study Needed?	Depends on scenario			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline Switching Study	Change Scenario No Switching Study	Difference
Total Cost ($ Million)	All	$149.49 ($102.5, $231.0)	$135.35 ($90.1, $206.2)	-9.4% (-12.1%, -7.9%)
Total Expected Cost ($ Million)		$217.06 ($133.9, $335.8)	$199.24 ($118.3, $304.6)	-8.2% (-11.7%, -6.8%)
Total Capitalized Cost ($ Million)		$249.40 ($155.9, $392.3)	$212.18 ($130.5, $329.1)	-14.5% (-18.5%, -12.2%)
Total Expected Capitalized Cost ($ Million)		$385.78 ($211.2, $597.7)	$331.59 ($177.6, $508.0)	-13.6% (-17.6%, -11.4%)
Total Expected Drug Development Duration (Years)		11.7 (9.5, 14.4)	10.6 (8.6, 12.7)	-9.2% (-11.8%, -8.2%)
Total Expected Lifetime Revenues (Million $)	1	$10,847.78 ($3,127.5, $44,624.4)		No Change
	2	$7,157.17 ($2,063.5, $29,442.4)		
	3	$3,772.73 ($1,087.7, $15,519.9)		
	4 or 5	$1,855.82 ($535.1, $7,634.3)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$9,823.32 ($2,832.1, $40,410.1)		No Change

	2		$6,421.03 ($1,851.2, $26,414.1)	
	3		$3,376.09 ($973.4, $13,888.2)	
	4 or 5		$1,656.58 ($477.6, $6,814.7)	
ENPV over Biosimilar Product's Lifetime (Million $)	1	$9,437.54 ($2,505.8, $39,919.6)	$9,491.73 ($2,543.7, $40,002.8)	1.0% (0.2%, 2.8%)
	2	$6,035.25 ($1,524.9, $25,923.6)	$6,089.43 ($1,562.8, $26,006.8)	1.6% (0.2%, 4.6%)
	3	$2,990.31 ($664.7, $13,397.7)	$3,044.50 ($699.2, $13,480.9)	3.7% (0.5%, 11.5%)
	4 or 5	$1,270.80 ($124.3, $6,324.2)	$1,324.99 ($202.9, $6,407.4)	15.0% (1.0%, 72.8%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

6.1.2 Patent Thickets

Patent thicket, sometimes called a patent "estate" or portfolio, is a term frequently used to describe the large number of patents—ranging from several dozen to multiple hundreds—taken out by some RP manufacturers in an effort to forestall or intimidate potential biosimilar competition, thereby extending their RP's exclusive presence in its U.S. market beyond the 20 years provided by U.S. and most international patent laws. Participants and observers of "patent thicketing" agree that the complexities of designing, manufacturing, testing, storing, transporting, and delivering into the body medications derived by manipulating the genetic structure of living cells comprise an opportunity to take out numerous patents. For biologics, patents taken out fall into several categories, including composition of matter (a primary patent); method(s) of use (e.g., treatment of one or more specific diseases); process or manufacturing patents; formulation patents, which claim a dosage form, route of administration, or new strength, etc.; and device patents covering a novel method for administering the biologic to the patient. Patents can be applied for, and are often granted, for several aspects of a new biologic. Primary patents are those that cover the active pharmaceutical ingredient and are usually the first patent that uses the name of the RP. Table 32 and Table 33 summarize patent thicket data compiled by I-MAK for top-selling biologics in 2017 and 2021.

> *[C]onstructed barriers to biosimilar market entry...are barriers intentionally established by market participants in order to block competition. Chief among these constructed barriers are patent thickets* [100].

Table 32. Patent Activity by 8 Top-Selling Biologic Reference Products of 2017 and Current Number of Competing Biosimilars

Proprietary name (proper name) (Company)	Therapeutic Area	Total Patent Applica-tions [a]	First Year Marketed in U.S.	Potential Total Years of Exclusivity	Number of Biosimilars in Market, 08/2024	Price Change, 2012–2017
Humira (adalimumab) (AbbVie)	Autoimmune Diseases	247	2002	39	10	144%

Proprietary name (proper name) (Company)	Therapeutic Area	Total Patent Applica-tions [a]	First Year Marketed in U.S.	Potential Total Years of Exclusivity	Number of Biosimilars in Market, 08/2024	Price Change, 2012–2017
Rituxan (rituximab) (Genentech)	Oncology	204	1997	47	3	25%
Enbrel (etanercept) (Amgen)	Autoimmune Diseases	57	1998	39	[b] 0	155%
Herceptin (trastuzumab) (Genentech)	Oncology	186	1998	48	6	-58%
Remicade (infliximab) (Janssen Biotech)	Autoimmune Diseases	123	1998	32	3	18%
Avastin (bevacizumab) (Genentech)	Oncology	219	2004	43	5	16%
Eylea (aflibercept) (Regeneron)	Ophthalmology	67	2011	34	[c] 0	6%
Lantus (insulin glargine) (Sanofi)	Diabetes	74	2000	37	2	114%

Source: I-MAK [96]
[a] Includes accepted applications and active applications.
[b] Two biosimilars, Erelzi and Eticovo, are under permanent injunction to stay out of the U.S. market until 2029.
[c] Three interchangeables, Opuviz, Yesafili, and Enzeevu, were approved by FDA in 2024 and are in litigation.

Table 33. Patent Profiles of 6 Top Selling Biologics of 2021

Reference Product	Total Applications Filed	Filed Before FDA Approval	Filed After FDA Approval	Active	Pending	Primary Patent Effective Filing Date	Primary Patent Expiration	Last Patent Expiration [a]
Enbrel (etanercept) (Amgen)	154	16	138	44	51	9/12/1989	4/24/2029	10/2037
Eylea (aflibercept) (Regeneron)	134	46	88	63	28	5/7/1996	5/24/2016	8/18/2040
Humira (adalimumab) (AbbVie)	311	24	287	134	4	8/7/1989	8/7/2010	3/13/2034
Keytruda (pembrolizumab) (Merck)	180	69	111	73	51	3/7/2001	5/28/2022	6/26/2039
Stelara (ustekinumab) (Janssen Biotech)	76	19	57	16	21	3/24/2000	3/24/2020	9/24/2039
Trulicity (dulaglutide) Eli Lilly	57	8	49	14	36	6/12/2003	12/7/2027	10/11/2038
Total	912	182	730	344	191			
Average	152	30	122	57	32			

Source: I-MAK [96]
[a] Excludes device patents.

6.1.2.1 The Patent Dance

BPCIA Litigation

Biosimilar litigation under BPCIA is crucial because it sets the legal framework for how and when biosimilars can enter the market. BPCIA offers an abbreviated approval pathway for biosimilars (also see Section 1), requiring them to engage in a “patent dance” with the RP sponsor to identify and resolve relevant patents before commercialization. This process clarifies

the timing and conditions for market entry, allowing biosimilar developers to address patent barriers in a structured way. Additionally, BPCIA litigation strikes a balance between innovation and competition by protecting the interests of biologic innovators while also providing a pathway for biosimilars to challenge those patents and compete in the market. Court decisions interpreting key BPCIA provisions, such as notice requirements or the scope of the "patent dance," create industry-wide precedents. These precedents guide future biosimilar developers, shape commercial strategies, and ultimately influence the speed at which patients gain access to biosimilars. In this way, BPCIA litigation not only resolves individual patent conflicts but also defines how innovation and competition coexist in the evolving biosimilar markets.

Specifically, BPCIA provides innovator companies with 12 years of market exclusivity after their original biologic is approved by FDA. Although biologic manufacturers normally apply for and are granted numerous patents on their innovative products, the 20 years of protection that patents provide is eroded by two factors: (1) to protect their biotechnology during years of development and clinical studies, patent applications are often submitted years before the candidate biologic is approved and marketed; and (2) biosimilar companies may identify weaknesses in the applicable patents and decide to enter the market and risk legal action against them alleging patent infringement.

Recognizing this, BPCIA provides innovator biologics with 12 years of exclusive presence in their markets, free from biosimilar competition, after they are approved. After that period, and after approval by FDA, biosimilars are free to enter the market at risk once they are approved by FDA. Like the Hatch-Waxman Act, BPCIA established a pro forma act of patent infringement to which the patent holder can respond to preserve their patent protections. The first legal complaint for patent infringement against a biosimilar was filed in March 2014 (Amgen v. Sandoz) against Zarxio, a biosimilar of Neupogen and the first biosimilar approved by CDER. Sandoz, the biosimilar manufacturer, won a summary judgment and finally launched Zarxio four years after the suit was filed. Since then, as of November 20, 2023, a total of 39 BPCIA-related lawsuits have been filed pitting RP companies against biosimilar companies—38 of them with the RP company as plaintiff [64].

The numerous lucrative biologics markets plus the abbreviated biosimilar approval pathway created by BPCIA were expected to attract companies into attempting early market entry, thereby risking legal action for patent infringement by RP companies. The BPCIA tried to impose some order on these legal actions, and possibly save some time, by prescribing a voluntary series of steps through which both parties would reveal the essentials of their legal arguments. The basic steps of the "patent dance," as it soon became known, are the following:

- After the biosimilar application is accepted by FDA, but 180 days prior to marketing, the applicant must disclose the application to the original BLA holder.
- The original BLA holder then has 60 days to provide the follow-on applicant with a list of patents.
- The applicant then has 60 days to respond with detailed statements as to why the patent(s) are either invalid, unenforceable, or will not be infringed by their product and a counter list of patents.

- This is then followed by a further response and negotiation period before the BLA holder can file a lawsuit.[39]

One early legal analyst of the patent dance observed, "[T]here can be little doubt that the complexities and potential gamesmanship that may emerge could rival those of the Hatch-Waxman regime" [97]. More recent analyses confirm that this gamesmanship has taken place in at least some instances [98]. Van de Wiele et al. [99] reported that 21 biosimilars that had been involved in patent litigation at the time of their research received FDA approval an average of 18.5 years after approval of the RP. The other seven biosimilars were approved 18.1 years after the RP, on average.

Table 34 summarizes the outcomes of BPCIA patent litigation filed in federal district court from October 2014 through November 20, 2023. The principals and some details regarding each case are presented in Table 35, derived from information provided by Goodwin [64]. There have been 39 filings involving 37 biosimilars and 14 RPs (Table 34).

Table 34. Summary of BPCIA Patent Infringement Litigation Filed as of November 20, 2023

Biosimilar Litigation Outcomes	Count	Percent
Reference product company prevailed	**3**	7.7%
Biosimilar company prevailed	8	20.5%
Cases settled	23	59.0%
Cases pending a decision (includes 1 awaiting trial in 2025)	5	12.8%
Total	[a] 39	100.0%
Cases appealed by RPC	7	17.9%
Cases appealed by Biosimilar	3	7.7%
Successful appeals	0	0.0%
Biosimilar Status		
Approved & launched in United States	19	51.4%
Approved, not (yet) launched in United States	5	13.5%
Not approved, not launched	13	35.1%
Total	[a] 37	100.0%

RPC = reference product company

Sources: [64] BPCIA Litigations; FDA Purple Book.

[a] Two cases, Alvotech USA v. Abbvie and Amgen v. Accord, involved biosimilars that were the subjects of two other dispositive cases. Hence, there were 39 cases involving 37 biosimilars and 15 reference products.

Four of the 13 biosimilars not yet approved by FDA have court cases still pending. These are CT-P42 and M710 (RP Eylea), Denosumab biosimilar (RP Prolia/Xgeva), and DRL_RI (RP Rituxan). Eight others settled their cases before their BLA submissions were approved (some of these had to remedy deficiencies pointed out by FDA in a complete response letter). Eleven cases resulted in court decisions. Eight of these favored the biosimilar company, including four findings of non-infringement or patent invalidity; three rulings accepted a voluntary dismissal, stipulation of non-infringement, and denial of a preliminary injunction; and one decision granted the biosimilar a change in venue, which led to a settlement. Three decisions favored the RP company. Two of these involved Eticovo and Erelzi, biosimilars of Enbrel, which, despite

[39] This list does not do justice to the details and complexity of the patent dance. See McGlynn et al. [150] for a fuller description.

approval by FDA, will wait until Enbrel's patents expire in 2029 to enter the U.S. market. In the third case, Amgen v. Hospira (Pfizer), the jury awarded $70 million to Amgen because Hospira created a commercial stockpile of their biosimilar of Epogen in preparation for launch, which is considered an act of infringement.

Manufacturers of all the RPs listed in Table 35 have attempted to prevent or delay marketing of biosimilars or tried to recover damages due to patent infringement. These cases highlight what is at stake for both parties in such litigation. As mentioned above, Amgen's subsidiary Immunex, the Enbrel patent holder, was successful against both Erelzi (Sandoz) and Eticovo (Samsung Bioepis), thereby keeping both of these CDER-approved biosimilars out of the market until at least 2029. Enbrel averaged $9.1 billion in annual sales over the four years from October 2018 to September 2022 (IQVIA, 2023), an average of $751.1 million per month.

Overall, based on these past results, the biosimilar companies have reason to be optimistic about their chances when entering BPCIA litigation. However, a positive court decision or successful settlement negotiation is not a guarantee of market entry. While 19 of these 37 biosimilars have been approved by FDA and launched into their markets, 13 biosimilars won or settled their cases, but were not yet approved by FDA. Five other biosimilars were approved but have not yet launched. Two others that were FDA-approved in November 2023, have not yet launched but have announced intentions to begin marketing in 2024. The most recently approved of these products that has not yet been launched is Tyruko, which Sandoz has said they are determined to launch before Jan. 1, 2025.

Among these 39 lawsuits, three filed in 2023 and one in 2022 are still pending. As can be seen in Table 35, the results of the other 35 are mixed. Eighteen were settled, nine resulted in victory for the defendants, three saw the plaintiffs prevail, and in one of the latter, the plaintiff was awarded $70 million in damages due to patent infringement.

Table 35. BPCIA Patent Litigation: Filings and Outcomes, October 24, 2014 – November 20, 2023

ID	Litigation	Biosimilar Name	Molecule Name	Status	Reference Product	Litigation Filed	District Court Outcome	Appellate Court Outcome
1	Amgen v. Sandoz, 2:23-CV-02406 (D. N.J.)	JUBBONTI/WYOST	denosumab	not approved	XGEVA; PROLIA	5/1/2023	Pending	n/a
2	Genentech et al. v. Biogen MA and Bio-Thera Solutions 1:23-cv-11573 (D. Ma.)	TOFIDENCE	tocilizumab-bavi	approved, not yet launched	ACTEMRA	7/13/2023	October 23, 2023, Settled	n/a
3	Genentech v. Amgen, Nos. 17-1407, -1471, 19-602 (D. Del.)	MVASI	bevacizumab-amvb	approved & launched	AVASTIN [litigation #1]	10/6/2017	July 19, 2019, Genentech's motions for a PI and TRO denied. July 7, 2020, Settlement	Denial of PI affirmed on interlocutory appeal
4	Genentech v. Samsung Bioepis. No. 20-859 (D. Del.)	SB8	bevacizumab biosimilar	not approved	AVASTIN [litigation #3]	6/28/2020	September 7, 2022, Voluntarily dismissed	n/a
5	Genentech v. Pfizer, No. 19-638 (D. Del.)	ZIRABEV	bevacizumab-bvzr	approved & launched	AVASTIN [litigation #2]	4/5/2019	September 20, 2019, Settled	n/a
6	Genentech v. Centus, No. 20-361 (E.D. Tex.)	FKB238	bevacizumab biosimilar	not approved	AVASTIN [litigation #4]	11/12/2020	July 2, 2021, Settled	n/a
7	Immunex v. Sandoz. No 16-01118 (D.N.J.)	ERELZI	etanercept-szzs	approved, not yet launched	ENBREL [litigation #1]	2/26/2016	August 9, 2019, Judgment of infringement and no invalidity in favor of Immunex	July 1, 2020, Affirmed by Fed. Cir.
8	Immunex v. Samsung Bioepis, No. 19-11755 (D.N.J.)	ETICOVO	etanercept-ykro	approved, not launched	ENBREL [litigation #2]	4/29/2019	November 3, 2021, Final Judgment and Order of Permanent Injunction against Samsung	n/a
9	Amgen v. Hospira, No. 15-839 (D. Del.)	RETACRIT	epoetin alfa-epbx	approved & launched	EPOGEN/PROCRIT [litigation #1]	9/18/2015	September 22, 2017, Jury found infringement and awarded Amgen $70M: Hospira's	Affirmed by Fed. Cir. March 16, 2020, rehearing denied.

ID	Litigation	Biosimilar Name	Molecule Name	Status	Reference Product	Litigation Filed	District Court Outcome	Appellate Court Outcome
							post-trial motions denied	
10	Regeneron v. Mylan No. 1:22-cv-00061 (D. Del.)	M710	aflibercept	not approved	EYLEA	8/2/2022	Pending	n/a
11	Regeneron v. Celltrion, 1:23-CV-00089 (N.D. W. Va.)	CT-P42	aflibercept	not approved	EYLEA	11/8/2023	Pending	n/a
12	Genentech v. Pfizer. No. 17-1672 (D. Del.)	TRAZIMERA	trastuzumab-qyyp	approved & launched	HERCEPTIN [litigation #1]	11/17/2017	December 4, 2018, Settled	n/a
13	Genentech v. Celltrion, Nos 18-095. -1025 (D. Del.)	HERZUMA	trastuzumab-pkrb	approved & launched	HERCEPTIN [litigation #2]	1/12/2018	December 27, 2018, Settled	n/a
14	Genentech v. Amgen, No. 18-924 (D. Del.)	KANJINTI	trastuzumab-anns	approved & launched	HERCEPTIN [litigation #3]	6/21/2018	July 19, 2019, Genentech's motions for a PI and TRO were denied. July 7, 2020, case settled.	Denial of PI affirmed on interlocutory appeal
15	Genentech v. Samsung Bioepis, No. 18-1363 (D. Del)	ONTRUZANT	trastuzumab-dttb	approved & launched	HERCEPTIN [litigation #4]	9/4/2018	July 1, 2019, Settled	n/a
16	Genentech, Inc. v. Tanvex Biopharma USA et al. No. 1:22-CV-0809 (S.D. Cal.)	TX05	trastuzumab	not approved	HERCEPTIN [litigation #5]	6/2/2022	February 1, 2023, Settled	n/a
17	Alvotech USA v. Abbvie, No. 2-21-00265 (E.D. Va.)	AVT02	adalimumab	not approved	HUMIRA	5/11/2021	October 22, 2021, Court allowed Alvotech's petition for change of venue to Illinois, leading to settlement.	n/a
18	AbbVie v. Alvotech, No. 21-2258, 21- 2899 (N.D. 3.)	AVT02	adalimumab biosimilar	not approved	HUMIRA [litigation #4]	4/27/2021, 5/28/2021	March 9, 2022, Settled	n/a

ID	Litigation	Biosimilar Name	Molecule Name	Status	Reference Product	Litigation Filed	District Court Outcome	Appellate Court Outcome
19	AbbVie v. Sandoz, No. 18-12668 (D.N.J.)	HYRIMOZ	adalimumab-adaz	approved & launched	HUMIRA [litigation #3]	8/10/2018	October 16, 2018, Settled	n/a
20	AbbVie v. Boehringer Ingelheim, No. 17-1065 (D. Del.)	CYLTEZO	adalimumab-adbm	approved & launched	HUMIRA [litigation #2]	8/2/2017	May 15, 2019, Settled	n/a
21	AbbVie v. Amgen. No. 16-666 (D. Del.)	AMJEVITA	adalimumab-atto	approved & launched	HUMIRA [litigation #1]	8/4/2016	September 28, 2017, Settled	n/a
22	Amgen v. Apotex, No. 15-61631 (S.D. Fla.) [consolidated with #5 below]	LAPELGA	pegfilgrastim	not approved	NEULASTA [litigation #1]	8/6/2015	September 6, 2016, non-infringement of '138 patent in favor of Apotex	2017 Non-infringement affirmed by Fed Cir.
23	Amgen v. Sandoz, No. 16-2581 (N.D. Cal.) [consolidated with #1 above]	ZIEXTENZO	pegfilgrastim-bmez	approved & launched	NEULASTA [litigation #2]	3/4/2016	December 19, 2017, Summary judgment of non-infringement in favor of Sandoz	May 8, 2019. Affirmed by Fed. Cir.
24	Amgen v. Accord (previously Apotex). No. 18-61828 (S.D. Fla.) [follow-on case]	LAPELGA GRASTOFIL	pegfilgrastim biosimilar; filgrastim biosimilar	not approved not approved	NEULASTA [litigation #1]; NEUPOGEN [litigation #2]	8/7/2018	November 15, 2019, Settled	n/a
25	Amgen v. Coherus. No. 17-546 (D. Del.)	UDENYCA	pegfilgrastim-cbqv	approved & launched	NEULASTA [litigation #3]	5/10/2017	March 27, 2018, Motion by Coherus to dismiss case granted.	April 19, 2023. Dismissal affirmed by Fed. Cir.
26	Amgen v. Hospira. No. 20-201 P. Del.)	NYVEPRIA	pegfilgrastim-apgf	approved & launched	NEULASTA [litigation #5]	2/11/2020	March 21, 2022, Settled	n/a
27	Amgen v. Mylan. No. 17-1235 (W.D. Pa.)	FULPHILA	pegfilgrastim-jmdb	approved & launched	NEULASTA [litigation #4]	9/22/2017	May 9, 2019, Stipulation of non-infringement	September 17, 2019. Fed. Cir. Endorses stipulation and proposed order of non-infringement of patent '997.
28	Amgen v. Apotex, No. 15-62081 (S.D. Fla.)	GRASTOFIL	filgrastim	not approved	NEUPOGEN [litigation #2]	10/2/2015	November 15, 2019, Settled	n/a

ID	Litigation	Biosimilar Name	Molecule Name	Status	Reference Product	Litigation Filed	District Court Outcome	Appellate Court Outcome
29	Amgen v. Kashiv (formerly Adello), No. 18-3347 (D.N.J.)	TPI G-CSF	filgrastim biosimilar	not approved	NEUPOGEN [litigation #3]	3/8/2018	November 25, 2019, Settled	n/a
30	Amgen v. Hospira, Nos. 18-1064, 20-561 (D. Del.)	NIVESTYM	filgrastim-aafi	approved & launched	NEUPOGEN [litigation #4]	7/18/2018	September 8, 2021, Settled	n/a
31	Amgen v. Sandoz, No. 14-474 (N.D. Cal.) [consolidated with #7 below]	ZARXIO	filgrastim- sndz	approved & launched	NEUPOGEN [litigation #1]	10/24/2014	March 19, 2015, Summary judgment of non-infringement in favor of Sandoz.	May 8, 2019. Affirmed by Fed. Cir.: Opinion modified on panel rehearing.
32	Amgen v. Tanvex, No. 19-1374 (S.D. Cal.)	NYPOZI	filgrastim	not approved	NEUPOGEN [litigation #5]	7/23/2019	Settled	n/a
33	Janssen v. Celltrion, No. 17-11008 (D Mass.)	INFLECTRA	infliximab-dyyb	approved & launched	REMICADE [litigation #1]	3/6/2015 (refiled 5/31/2017)	July 30, 2018, Summary judgment of invalidity as to '471 patent. Summary judgment of non-infringement as to '083 patent, subject to any appeal	March 5, 2020. Fed. Cir. dismissed Janssen's appeals of both summary judgments.
34	Janssen v. Samsung Bioepis, No. 17-3524 (D.N.J.)	RENFLEXIS	infliximab-abda	approved & launched	REMICADE [litigation #2]	5/17/2017	November 30, 2017, Parties agreed to Voluntary Dismissal with prejudice.	n/a
35	Genentech v. Sandoz. No. 17-13507 (D.N.J.)	GP2013	rituximab	not approved	RITUXAN [litigation #1]	12/21/2017	December 6, 2018, Settled	n/a
36	Genentech, Inc., Hoffmann-Roche Inc. and Biogen, Inc. v. Dr. Reddy's Labs, Inc., Fresenius Kabi USA, LLC	DRL_RI	rituximab	not approved	RITUXAN [litigation #3]	11/ 17/2023	Pending	n/a

ID	Litigation	Biosimilar Name	Molecule Name	Status	Reference Product	Litigation Filed	District Court Outcome	Appellate Court Outcome
	et al., 2:23-cv-22485 (D. N.J.)							
37	Genentech v. Celltrion, Nos.18-574. -11553 (D. N.J.)	TRUXIMA	rituximab- abbs	approved & launched	RITUXAN [litigation #2]	1/12/2018	November 1, 2018, Settled	n/a
38	Janssen v. Amgen No. 1:22-cv-0 1549 (D.Del.)	WEZLANA	ustekinumab-auub	approved, not yet launched	STELARA	11/29/2022	May 22, 2023, Settled	n/a
39	Biogen Inc. et al. v. Sandoz Inc. et al. No. 1:22-cv-1190 (D. Del.)	TYRUKO	natalizumab-sztn	approved, not yet launched	TYSABRI	9/19/2022	June 20, 2023, PI against Sandoz denied; trial set for May 5, 2025.	n/a

Legend: outcome favors Reference Product, outcome favors Biosimilar
n/a = not applicable; PI = preliminary injunction; TRO = temporary restraining order
Source: Goodwin, [64]. Big Molecule Watch. https://www.bigmoleculewatch.com/bpcia-patent-litigations/; FDA Purple Book.
Updated: November 20, 2023

Manufacturers of all the RPs listed in Table 35 attempted to prevent or delay marketing of biosimilars or tried to recover damages due to patent infringement. The results of the other 30 were mixed. Eighteen were settled, nine resulted in victory for the defendants, three saw the plaintiffs prevail, and in one of the latter, the plaintiff was awarded $70 million in damages due to patent infringement.

The other two victories by a plaintiff involved the same RP, Enbrel (etanercept), and highlight what is at stake for both parties in such litigation. Amgen's subsidiary Immunex, the Enbrel patent holder, was successful against both Erelzi (Sandoz) and Eticovo (Samsung Bioepis), thereby keeping both these CDER-approved biosimilars out of the market until at least 2029. Enbrel averaged $9.1 billion in annual sales over the four years from October 2018 to September 2022 (IQVIA, 2023), or $751.1 million per month.

Assessing the value to the RP of delaying biosimilar market entry by a month, quarter, or year requires a series of estimates based on IQVIA and other sales data. This would include projections of the market share of one or more entering biosimilars, the impact of biosimilar entry on the RP's price per unit, any possible negative impact on the value of the reference company's shares. One recent analysis [100] calculated that, for six biosimilars approved in the United States, the aggregate biosimilar market share went from approximately 8 percent three months after market entry to about 28 percent one year after entry.

Among the 27 biosimilars whose cases were either won or settled, the BLAs of eight biosimilars were not approved by CDER (see Table 36).

Table 36. Litigation Outcomes of Eight Biosimilars Not Approved by CDER

Unapproved Biosimilar	Biosimilar Manufacturer	Reference Product	Date of Complaint	Litigation Outcome
Lapelga	Apotex	Neulasta	08/06/2015	In favor of Apotex [a]
Grastofil	Apotex	Neupogen	10/02/2015	In favor of Apotex [a]
Lapelga & Grastofil	Accord (prev. Apotex)	Neulasta & Neupogen	08/07/2018	Settled [a]
GP2013	Sandoz	Rituxan	12/22/2017	Settled
TPI G-CSF	Kashiv	Neupogen	03/08/2018	Settled
TX-01	Tanvex	Neupogen	07/23/2019	Settled
SB8	Samsung Bioepis	Avastin	06/28/2020	Settled
FKB238	Centus	Avastin	11/12/2020	Settled
AVT02	Alvotech	Humira	05/28/2021	Settled

Source: [64]

[a] A follow-on case, Amgen v. Accord (previously Amgen v. Apotex), involving both Lapelga and Grastofil, was filed 08/07/2018 and subsequently settled.

BPCIA provides a well-scripted series of steps for the RP and biosimilar companies to follow that would facilitate a timely resolution of the kind of patent disputes that sometimes kept generic drugs out of a market for several years. These steps are summarized in Figure 9. The patent dance essentially limits the number of patents that can be asserted by the RP company to a number agreed to by the biosimilar company; replicates the results of the discovery process that normally would precede a trial; informs both sides of each other's arguments pertaining to each patent at issue; and prescribes a maximum time limit of 8.3 months (250 days) to complete this process.

The first step of the patent dance calls for the biosimilar company to provide its abbreviated biological license application to the RP company within 20 days of submitting it to FDA for review. An important intent of the patent dance is to limit the number of patents in suit (see Figure 9, steps 2–7, 10,11). Unless one or the other litigant withdraws from the dance, the biosimilar applicant has a say about which and how many patents are litigated. That said, if the RP company lists dozens of patents on the initial list it provides to the biosimilar applicant in steps 2 and 3 (the "3A list"), attorneys for the biosimilar company will have to expend some effort to explain why each of these patents is invalid, unenforceable, or why their biosimilar is non-infringing (step 5).

Figure 9. Steps Prescribed by BPCIA "Patent Dance" Intended to Facilitate Resolution of Disputes over the Validity, Enforceability, and Degree of Infringement of RPS Patents

Sequential Elements of the "Patent Dance"
Maximum time required—250 DAYS
Sources: Goodwin [149] Guide to the BPCIA's biosimilars patent dance;
McGlynn et al. [150] How biosimilars are approved and litigated: Patent dance timeline

FIRST WAVE LITIGATION

1. Biosimilar Applicant provides copy of their BLA and manufacturing information to the Reference Product Sponsor (RPS) (l)(2)(A)
2. RPS provides Applicant with list of potentially infringed patents (l)(3)(A)(i) 262(l)(3)(A) and § 262(l)(7)
3. RPS identifies any patents on list that RPS is willing to license to Applicant (l)(3)(A)(ii)
   NOTE: RPS must supplement its list with relevant newly issued or licensed patents within 30 days of issuance or licensing. Any newly issued or licensed patents listed on the RPS supplement will be subject to the second wave of patent litigation (l)(7)
4. NOTE: Applicant may provide RPS with list of patents Applicant believes could reasonably be asserted by RPS (l)(3)(B)(i)
5. Applicant responds to each patent on RPS's (l)(3)(A) list with: (i) Detailed statement of invalidity, unenforceability or noninfringement OR (ii) Statement that Applicant will not commercially market product before patent expiration (l)(3)(B)(ii)(I)-(II)
6. Applicant responds to RPS's licensing offers, if any (l)(3)(B)(iii)
7. RPS provides Applicant with detailed statement of validity, enforceability, and infringement for each patent for which Applicant has provided (l)(3)(B) detailed statement. § 262(l)(3)(C)

If parties agree on which patents to litigate § 262(l)(4)A, then:

8. RPS files First Wave Litigation § 262(l)(6)(A)-(B)
9. Applicant notifies FDA that suit has been filed § 262(l)(6)(C)

If parties do not agree on which patents to litigate §262 (l)(4)(B) then:

10. Applicant identifies the patents they believe should be litigated § 262(l)(5)(A)
11. Parties simultaneously exchange lists of patents to be litigated (l)(5)(B)(i)
    NOTE: The number of patents on RPS's list cannot exceed the number of patents on Applicant's list unless the Applicant has zero on its list, in which case RPS may list 1 patent (l)(5)(B)(ii)
12. RPS files First Wave Litigation § 262(l)(6)(A)-(B)
13. Applicant notifies FDA that suit has been filed § 262(l)(6)(C)

SECOND WAVE LITIGATION

After Applicant submits BLA to FDA:

14. Applicant provides RPS 180-day notice that it intends to commercially market its biosimilar (l)(8)(A), whereupon...
15. RPS can seek preliminary injunction prohibiting commercial launch of Applicant's product until court rules on any patents listed by RPS or Applicant in (l)(3) or (l)(7) that were not the subject of First Wave Litigation (l)(8)(B)

6.1.2.2 Impact of the Patent Dance on Patent Thickets

Sandoz sponsored the first biosimilar to be approved by FDA, Zarxio (filgrastim-sndz), and did not want to reveal its manufacturing process to Amgen, as required by the first step of the patent dance. Two years after Zarxio was approved and had entered the market, the Supreme Court, in Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664 (2017), held that Sandoz could not be forced by injunction to provide Amgen its BLA submission nor its manufacturing process. The court also found that Sandoz could give Amgen its notice of commercial marketing even before FDA accepted Sandoz' 351(k) BLA for evaluation.

The Court's decision essentially made the patent dance optional, thereby creating two broad classes of litigants: those who completed the patent dance and those that did not. Assessing the patent dance after Sandoz v. Amgen, Dong [101] examined 19 RP/biosimilar patent disputes filed from August 2017 to April 2021. In 12 instances, litigants effectively completed the patent dance; in seven cases one of the litigants—invariably the biosimilar applicant—withdrew from the process. Table 37 summarizes the author's data regarding the number of patents in suit among these cases. The data suggest that completing the patent dance correlates with limiting the number of patents in suit.

Table 37. Patent Dance Participation and Patents in Suit Among 19 Biosimilar Infringement Filings

Patent Dance Participation	Patent Cases	Patents in suit	Average patents in suit	Median patents in suit	IQR	Approved Biosimilars	Average months from court filing to launch	Median months from filing to launch
Completed	12	133	11.1	6	2 - 14	9	31.3	13.1
Incomplete	7	170	24.3	20	20 - 40	4	24.4	24.4

IQR = interquartile range
Source: [101]

As can be observed in Table 37, among the 19 patent cases in the author's study period, the number of patents in suit did not necessarily correlate with a briefer interval between the initial filing of the RP's action and the biosimilar product launch. It is noteworthy that six out of the 19 biosimilars involved in these cases—three in each category—have yet to be approved by FDA. Also, the median "months from court filing to launch" among the nine cases that completed the patent dance was just 13.1.

6.1.2.3 The Humira Patent Thicket

Humira has been among the best-selling and most lucrative pharmaceuticals in the United States every year since its approval by FDA on December 31, 2002. Abbvie has described its patents as including "one composition-of-matter patent on the active compound adalimumab, fourteen patents on its formulation, twenty-four patents on its method of manufacture, twenty-two patents on its seven therapeutic indications, and fifteen patents on 'other' components, such as associated devices and diagnostics" [102]. Abbvie's primary patent expired in 2016, but it retains 15 ancillary patents with expirations ranging from 2027 to 2034 [103].

AbbVie's 'patent estate' forms a patent thicket [around Humira] that makes it nearly impossible for a biosimilar to enter the market without risking massive infringement liability.

Geaghan-Breiner, 2020 [101]

[W]hat's wrong with having lots of patents? If AbbVie made 132 inventions, why can't it hold 132 patents?

Judge Frank Easterbrook, U.S. Court of Appeals, 7th Circuit

The patent thicket that Abbvie planted around Humira has prompted considerable comment and accusations of anti-competitive behavior. Judge Easterbrook's question, quoted above, came during an appeal of the lower court's dismissal of a class action suit brought by payers alleging that Abbvie's patent thicket and its settlement agreements with the sponsors of several Humira biosimilars violated the Sherman

Antitrust Act.[40] It is widely assumed that the sheer number of original biologic patents inhibits attempted market entry by some biosimilar companies [104]. While this may be true, given the limited number of biosimilars approved to date, a definitive empirical answer to this question remains elusive.

Judge Easterbrook's question also highlights the fact that, within the sphere of pharmaceutical patents, the U.S. Patent and Trademark Office (USPTO) and FDA operate in functional contradiction. However, both organizations acknowledge that it is the policy of the executive branch to optimize public health by maximizing patient access to life-saving medications. Currently, the government is focused on intensifying competition in chemical drug and biologic markets to lower the costs of high-priced medications [105]. Meanwhile, the patent system provides a period of exclusive market access to originators of patentable products and enables monopoly behaviors that can inhibit access to products crucial for maintaining good health.

Goode & Chao [106] compared the patent experiences of the first biosimilars to attempt to enter the markets of eight RPs in the United States, Canada, and the United Kingdom. Four of the RPs have evidently set about amassing U.S. patents. How these thickets affected the timing or number of biosimilar launches is less evident. The longest delay, 151 months, is related to Enbrel's assertion of just five patents (Enbrel won a permanent injunction preventing biosimilars Erelzi and Eticovo from entering the market until Enbrel's primary patents expire). Humira, the RP with the thickest thicket and most asserted patents in suit, confronts the most biosimilars of any RP.

Humira's experience with market share after biosimilar entry includes an apparently new development in this area. As noted, in 2023, 10 biosimilars to Humira were launched, three of them interchangeables. Yet, by early 2024, Humira maintained approximately 96 percent of adalimumab sales. This began to erode immediately in April 2024 after CVS Caremark, one of the three largest PBMs in the United States, removed Humira from its formulary, in favor of Hyrimoz, a biosimilar and recently designated interchangeable marketed by Sandoz and Cordavis.[41] As shown in Table 38, Hyrimoz achieved 13 percent market share within a month of Humira's removal from Caremark's formulary, and Humira's share dropped to 82 percent [107]. Reportedly, "new prescriptions for Hyrimoz skyrocketed, jumping from 640 in the week ending March 29 to 8,300 in the week ending April 5" [107]. By May 10, Humira's share of adalimumab prescriptions had fallen to 71.7 percent and seemed to stabilize at about that level for the next four weeks [108]. Meanwhile, Cordavis entered into an agreement with Abbvie to market an unbranded version of Humira (technically not a biosimilar, but comparable to an authorized generic in small moleule drug markets). That "Abbvie/Cordavis co-branded" adalimumab accounted for 8.6 percent of adalimumab prescriptions as of June 7.

[40] The settlements called for Humira biosimilars to enter the U.S. market at various times during 2023 and to pay royalties on their sales to Abbvie; meanwhile, Abbvie allowed the biosimilars to enter the EU market in 2018.
[41] CVS Health announced the launch of Cordavis in August 2023, saying its subsidiary "will work directly with manufacturers to commercialize and/or co-produce biosimilar products...{that] will be FDA approved, high quality and easy for patients to use and will help ensure consistent long-term supply of affordable biosimilars" [162].

Table 38. Weekly Percentage of Adalimumab Prescriptions Written for Reference Product (Humira) and Biosimilars

Week ending...	Abbvie (Humira)	Sandoz/Cordavis (Hyrimoz)	Abbvie/Cordavis (Co-branded)	All Other Biosimilars
1/5/2024	98.4%	NL	NL	<1.6%
3/29/2024	96.3%	<1%	NL	<1%
4/5/2024	84.5%	11.7%	NL	3.8%
4/12/2024	80.5%	15.0%	<1%	4.2%
4/19/2024	80.4%	11.8%	3.5%	4.3%
4/26/2024	76.6%	11.5%	7.6%	4.4%
5/3/2024	73.6%	14.7%	7.2%	4.5%
5/10/2024	71.7%	14.2%	9.9%	4.8%
5/17/2024	72.2%	13.4%	9.7%	4.9%
5/24/2024	72.0%	13.9%	9.3%	4.8%
5/31/2024	72.6%	13.6%	8.4%	5.1%
6/7/2024	72.3%	14.3%	8.6%	5.0%

NL = not launched

Source: Deutsche Bank and IQVIA, referenced in Fein [108], Figure 1.

Since then, Cigna/Express Scripts, the second-largest PBM, has followed Caremark by announcing that it would drop Humira from its largest commercial formularies beginning in 2025, and, through its subsidiary distributor Quallent, would offer four interchangeable biosimilars: Cyltezo and its unbranded version (adalimumab-adbm) from Boehringer Ingelheim; Simlandi from Teva; and adalimumab-adaz (unbranded Hyrimoz) from Sandoz [109].

Evernorth's announcement of the move explained its reasoning: "[N]ew interchangeable biosimilar treatments are readily available. After years of delays caused by patent thickets, biosimilars are at last disrupting a class of medications that for too long has been controlled by several brand-name biologics like Humira" [109].

As for Optum Rx, the third largest PBM, it announced in August 2024 that it would exclude branded Humira for new patients starting in January 2025. Patients taking Humira could continue to do so "with improved Humira pricing." Optum explained: "We have chosen to wait on preferring only Humira biosimilars until all drug strengths are interchangeable at the pharmacy without a new prescription, which is expected later in 2025" [110].[42]

On July 9, 2021, President Biden issued the *Executive Order on Promoting Competition in the American Economy*, in which he stated, "Americans are paying too much for prescription drugs and healthcare services — far more than the prices paid in other countries. ...And too often, patent and other laws have been misused to inhibit or delay — for years and even

[42] The emphasis placed on the availability of interchangeables for Humira as prompting the exclusion of the RP from major formularies may have distracted from other more political reasons for the move. PBMs have been the target of much criticism and proposed legislation to inhibit their power to negotiate in secret and receive manufacturer rebates; to limit manipulation of formulary tiers (so that more expensive brand drugs have the same or lower copays than drugs with lower list prices).

decades — competition from generic drugs and biosimilars, denying Americans access to lower-cost drugs."

This executive order called for a "whole of government" effort to deal with the imbalances caused by over-consolidation in many industries. In response, the Director of the USPTO wrote to the Commissioner for Food and Drugs and attached the *USPTO Initiatives on Drug Pricing* [111]. Germane to patent thickets, among the initiatives listed was: "The USPTO will explore whether any changes need to be made to the patent system regarding obviousness-type double patenting." The reason given for this exploration of potential changes was that "...multiple patents directed to obvious variants of an invention could potentially deter competition if the number of patents is prohibitively expensive to challenge in post-grant proceedings before PTAB and in district court. And later issued patents to obvious variants may delay resolution of ongoing district court litigation thereby potentially delaying generic and biosimilar entry into the market" [111].

Goode, Feldman, and Tu [103] analyzed patents litigated by RP manufacturers from 2010 to 2023. During their study period, 12 original biologics filed suit against 48 biosimilars involving 271 total patents, "of which 12 (4 percent) were primary, 22 (8 percent) ancillary secondary, and 237 (87 percent) nonancillary secondary patents. Ancillary product patents were filed a median of 18.3 years (IQR, 17.4–19.6 years) after the first primary patent was filed and extended the expected duration of protection by a median of 10.4 years (range, 2.4–17.9 years) beyond the primary patents" [103].

6.1.2.4 Recent major court decisions

Skinny Labeling and Induced Infringement: GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1327 (Fed. Cir. 2021).

One method generics and biosimilars have available to enter a patent-protected RP market is to apply for approval of a use or uses not protected by any RP patent. In effect, the generic or biosimilar carries a label that "carves out" patent-protected uses of the RP and is thereby able to argue that their product is non-infringing.[43] Colloquially called skinny labeling, this procedure is established in 21 U.S.C. § 355(j)(2)(A)(v3) and is also referred to as a "section v3 carveout." Skinny labeling has been an important mechanism for bringing biosimilars to market despite the presence of numerous RP patents. A study of the practice by Egilman et al. reported that 22 out of 33 biosimilars (67 percent) approved by FDA from 2015 through 2021 had skinny labels, and that, of 21 biosimilars marketed before 2022, 13 (62 percent) were launched with a skinny label [112].

In this context, the decision in GlaxoSmithKline LLC (GSK) v. Teva Pharms. USA, Inc. was seen by manufacturers and legal observers as potentially undermining an important avenue for biosimilar market entry. Briefly, the GSK v. Teva litigation concerned Teva's use of a skinny label to bring to market its generic version of Coreg, GSK's blockbuster heart drug. GSK sued Teva, arguing that the generic's label and Teva's instructions induced physicians to infringe GSK's

[43] In part, the practical utility of this tactic rests upon the willingness of physicians to prescribe generic medications to treat conditions for which they are not approved.

patents. A jury agreed with GSK, awarding the brand company damages of $235 million. This judgment was thrown out by the trial judge in response to Teva's motion for a judgment as a matter of law. The Court of Appeals for the Federal Circuit reversed the trial judge and reinstated the jury verdict.

The court of appeals vacated their previous decision and reheard the case after the Supreme Court refused certiorari. While they again reinstated the jury's decision, they sought to address the concerns expressed in the minority opinion of the dissenting judge and by numerous amici who viewed their decision as a serious barrier for future application of skinny labeling.[44] Since then, other observers have interpreted district court decisions on skinny labeling cases—some of which found non-infringement in cases similar to GSK v. Teva—as mitigating the alarms set off by GSK v. Teva; see, for instance, Foley Hoag [113].

Mayor and City Council of Baltimore v. AbbVie, Inc., No. 20-2402 (7th Cir. August 1, 2022)

The lawsuit against Abbvie by the City of Baltimore et al., and Baltimore's subsequent appeal, constitute a bulwark for RPCs that desire to maintain as long as possible the enormous revenue streams that blockbuster biologics provide. Among other issues, the court apparently ignored the unusual power that a monopoly gives a drug manufacturer over "consumers" and their insurers. The court compared Abbvie's amassing of patents to firms in the electronics and technology industries, failing to observe the important role that licensing plays in technology manufacturing, as opposed to the pharmaceutical industry, where licensing plays little role—except occasionally as a bargaining chip in settlement negotiations [114]. Finally, the court has been criticized—see, e.g., Knox & Curfman, [115]—for misapplying the Noerr-Pennington Doctrine, which provides immunity from antitrust actions to those who are "petitioning the federal government"—which is how the court characterized applying for a patent. The court also rejected a pay-for-delay argument regarding the settlements in which Abbvie allowed the Humira biosimilars to enter the EU market in 2018—five years before the settlement allowed them to enter the U.S. market. The court reasoned that, because no money changed hands, and because the biosimilars were to enter each market before the expiration of the next patent, there was no pay-for-delay [115].

Aside from the 84 patents claimed by Abbvie itself, descriptions of the Humira patent thicket in published studies have put the number of patents at or above 132 [115]; these 132 patents are the product of 247 applications.

6.1.2.5 How much do RP Patents Delay Biosimilar Market Entry?

Table 39, presents the BLA submission dates, FDA approval dates, and market launch dates for the first biosimilars to enter, or in the case of Eylea, attempt to enter, their RP markets. The time intervals in months between these events are also calculated. Enbrel is not

[44] The 2-1 majority opinion "...repeatedly stressed that the case should be interpreted considering its specific facts and not as a change to the law of induced infringement. Judge Prost [the dissenting judge] again filed a lengthy dissent, contending that the new opinion does not resolve the concerns caused by the court's prior opinion, and that it will still leave significant risk and uncertainty for generic drug manufacturers who follow a skinny label route to approval" [152]

represented because the loophole in the USPTO rules that allowed Enbrel's primary patent to be extended to 2029 has been closed. Including the 87.5-month interval between Amjevita's BLA submission and the market entry date provided in its settlement agreement with Abbvie, the average time interval from first BLA submission to market launch is 30.4 months and the median is 26.0 months. In some instances, the biosimilar applicant has had to resubmit its BLA or file extensive amendments per FDA's request. If we use the dates when resubmissions and amendments were finalized, rather than the initial submission dates, the average interval between submission and launch is 22.0 months.

These figures compare favorably with the mandated 30-month delay before FDA approval that a generic drug applicant endures after submitting a paragraph IV certification that their product does not infringe the brand drug's patents or that these patents are invalid. It is true that the 12-year regulatory exclusivity enjoyed by biologic RPs often means that their primary composition of matter patents are nearing expiration (as the originator company usually applies for such patents several years before FDA approval). Under these circumstances the RPC may be more inclined to negotiate a settlement than to defend secondary patents that may be less robust.

Table 39. Timelines for First-approved Biosimilars in 16 U.S. Biologic Markets [a]: Intervals between BLA submission, FDA approval, and Market entry.

First-approved Biosimilar	Reference product	Non-proprietary name	Biosimilar's Initial BLA Submission	Date of Resubmission or major amendments to BLA	FDA approval	Commercial launch	Months [b] from BLA submission to approval	Months from BLA submission to launch	Months from Resubmission or major BLA amendments to launch
AMJEVITA (Amgen)	Humira (AbbVie)	adalimumab-atto	25-Nov-2015	n/a	23-Sep-2016	31-Jan-2023	10.1	87.5	n/a
YESAFILI (Mylan)	Eylea (Regeneron)	aflibercept-jbvf	29-Oct-2021	27-Nov-2023	20-May-2024	n/a permanent injunction pending appeal	31.1	n/a permanent injunction pending appeal	n/a permanent injunction pending appeal
MVASI (Amgen /Allergan)	Avastin (Roche / Genentech)	bevacizumab-awwb	14-Nov-2016	n/a	14-Sep-2017	18-Jul-2019	10.1	32.5	n/a
JUBBONTI/WYOST (Sandoz)	Prolia/Xgeva (Amgen)	denosumab-bbdz	5-Dec-2022	17-Nov-2023	5-Mar-2024	19-Feb-2025	15.2	26.9	15.3
BKEMV (Amgen)	Soliris (Alexion)	eculizumab-aeeb	28-Feb-2023	27-Feb-2024	28-May-2024	1-Mar-2025	15.2	24.4	12.3
RETACRIT (Pfizer/Hospira)	Epogen/ Procrit (Amgen/ Johnson & Johnson)	epoetin alfa-epbx	16-Dec-2014	22-Dec-2016; 17-Nov-2017	15-May-2018	12-Nov-2018	41.1	47.6	11.8
ZARXIO (Sandoz)	Neupogen (Amgen)	filgrastim-sndz	8-May-2014	5-Mar-2015	6-Mar-2015	Sep-2015	10.1	16.0	6.0
INFLECTRA (Pfizer /Celltrion	Remicade (Johnson & Johnson/ Janssen)	infliximab-dyyb	8-Aug-2014	5-Oct-2015	5-Apr-2016	Nov-2016	20.2	27.2	13.1
SEMGLEE Interchangeable (Mylan/Viatris / Biocon)	Lantus (Sanofi)	insulin glargine-yfgn	29-Jul-2020	n/a	28-Jul-2021	16-Nov-2021	12.1	15.8	n/a
TYRUKO (Sandoz)	Tysabri (Biogen)	natalizumab-sztn	24-May-2022	17-Feb-2023	24-Aug-2023	6-May-2024	15.2	23.8	14.8
FULPHILA (Mylan/Biocon)	Neulasta (Amgen)	pegfilgrastim-jmdb	9-Dec-2016	4-Dec-2017	4-Jun-2018	26-Jul-2018	18.1	19.8	7.8
BYOOVIZ Interchangeable (Samsung Bioepis / Biogen)	Lucentis (Roche / Genentech)	ranibizumab-nuna	17-Sep-2020	n/a	17-Sep-2021	2-Jun-2022	12.2	20.8	n/a
TRUXIMA (Celltrion /Teva)	Rituxan (Roche /Genentech)	rituximab-abbs	28-Apr-2017	29-May-2018	28-Nov-2018	11-Nov-2019	19.3	30.9	17.7
TOFIDENCE (Biogen/Bio-Thera)	Actemra (Roche / Genentech)	tocilizumab-bavi	29-Sep-2022	Yes [c]	29-Sep-2023	6-May-2024	12.2	19.5	n/a

First-approved Biosimilar	Reference product	Non-proprietary name	Biosimilar's Initial BLA Submission	Date of Resubmission or major amendments to BLA	FDA approval	Commercial launch	Months [b] from BLA submission to approval	Months from BLA submission to launch	Months from Resubmission or major BLA amendments to launch
OGIVRI (Mylan)	Herceptin (Roche /Genentech)	trastuzumab-dkst	3-Nov-2016	28-Jul-2017	1-Dec-2017	2-Dec-2019	13.1	37.5	28.6
WEZLANA (Amgen)	Stelara (Johnson & Johnson/ Janssen)	ustekinumab-auub	31-Oct-2022	Yes [c]	31-Oct-2023	No later than Jan. 1, 2025, per settlement	12.2	26.0	n/a
		Mean			16.7		30.4		21.2
		Median			14.2		26.0		15.8

n/a = not applicable; BLA = biologics license application
[a] There are 16 markets represented rather than 18 because (1) the USPTO policy that enabled Enbrel's primary patent to be extended to 2029 is no longer in effect and thus will not affect any future patent negotiations; and (2) for this table, the two denosumab biosimilars, Jubbonti and Wyost, are being treated as one market entrant.
[b] One month = 30 days
[c] "Yes" = FDA's approval letter indicated that it had requested and received amendment(s) to the BLA, but the letter did not give a date when these were received, nor did the request result In a delay of approval.
Sources: submission and approval dates, Drugs@FDA.gov; launch dates, various pharma websites and company press releases.

Table 40. Patent Infringement Cases Filed by Biologic Reference Product (RP) Manufacturers

Reference Product (RP) Proper Name	Litigation	Biosimilar (proper name) [status]	Reference Product Name	Date Litigation Filed	Number of Patents Asserted	District Court Outcome	Appellate Court Outcome
Adalimumab	Alvotech USA v. Abbvie, No. 2-21-00265 (E.D. Va.)	ATV02 (adalimumab) [not approved]	HUMIRA	5/11/2021	3	October 22, 2021, Allowed Alvotech's petition for change of venue to Illinois	n/a
Adalimumab	AbbVie v. Amgen. No. 16-666 (D. Del.)	AMJEVITA (adalimumab-atto) [approved & launched]	HUMIRA [litigation #1]	8/4/2016	61	September 28, 2017, Settled	n/a
Adalimumab	AbbVie v. Boehringer Ingelheim, No. 17-1065 (D. Del.)	CYLTEZO (adalimumab-adbm) [approved & launched]	HUMIRA [litigation #2]	8/2/2017		May 15, 2019, Settled	n/a
Adalimumab	AbbVie v. Sandoz, No. 18-12668 (D.N.J.)	HYRIMOZ (adalimumab-adaz) [approved & launched]	HUMIRA [litigation #3]	8/10/2018	2	October 16, 2018, Settled	n/a
Adalimumab	AbbVie v. Alvotech, No. 21-2258, 21- 2899 (N.D. 3.)	AVT02 (adalimumab biosimilar) [not approved]	HUMIRA [litigation #4]	4/27/2021, 5/28/2021	1st litigation, 4 asserted; Subsequent round, 62	March 9, 2022, Settled	n/a
Aflibercept	Regeneron v. Mylan No. 1:22-cv-00061 (D. Del.)	YESAFILI (aflibercept-jbvf) [formerly M710]	EYLEA	8/2/2022	24 patents at suit: 7 for methods of administering dosing schedules; 3 formulation patents; 14 manufacturing patents	Pending. Permanent injunction in favor of Regeneron issued June 11, 2024	n/a
Aflibercept	Regeneron v. Celltrion, 1:23-CV-00089 (N.D. W. Va.)	CT-P42 (aflibercept) [not approved]	EYLEA	11/8/2023	11	Pending	n/a
Aflibercept	Regeneron v. Samsung Bioepis Co., Ltd., 1:23-CV-00094 (N.D. W. Va.)	OPUVIZ (aflibercept-yszy)	EYLEA	11/22/2023	13	Pending	n/a
Aflibercept	Regeneron v. Formycon AG, 1:23-CV-00097 (N.D. W. Va.)	FYB203 (aflibercept) [not approved]	EYLEA	11/29/2023	13	Pending	n/a
Aflibercept	Regeneron v. Amgen Inc., 2-24-cv-00264 (C.D. Cal.)	ABP 938 (aflibercept) Not approved	EYLEA	1/10/2024	13	Pending	

Reference Product (RP) Proper Name	Litigation	Biosimilar (proper name) [status]	Reference Product Name	Date Litigation Filed	Number of Patents Asserted	District Court Outcome	Appellate Court Outcome
	(transferred to N.D. W.Va., C.A. 1:24-cv-00039)						
Bevacizumab	Genentech v. Amgen, Nos. 17-1407, -1471, 19-602 (D. Del.)	MVASI (bevacizumab-amvb) [approved & launched]	AVASTIN [litigation #1]	10/6/2017	24	July 19, 2019, Genentech's motions for a preliminary injunction and TRO denied. July 7, 2020, Settlement	Denial of PI affirmed on interlocutory appeal
Bevacizumab	Genentech v. Pfizer, No. 19-638 (D. Del.)	ZIRABEV (bevacizumab-bvzr) [approved: launched]	AVASTIN [litigation #2]	4/5/2019	22	September 20, 2019, Settled	n/a
Bevacizumab	Genentech v. Samsung Bioepis. No. 20-859 (D. Del.)	SB8 (bevacizumab biosimilar) [not approved]	AVASTIN [litigation #3]	6/28/2020	14 (5)	September 7, 2022, Voluntarily dismissed	n/a
Bevacizumab	Genentech v. Centus, No. 20-361 (E.D. Tex.)	FKB238 (bevacizumab biosimilar) [not approved]	AVASTIN [litigation #4]	11/12/2020	10	July 2, 2021, Settled	n/a
Denosumab	Amgen v. Sandoz, 2:23-CV-02406 (D. N.J.)	JUBBONTI WYOST (denosumab-bbdz) approved Interchangeable biosimilar	XGEVA PROLIA	5/1/2023	21	April 29, 2024, Settled, Sandoz stipulates that they infringed 2 patents, enjoined from marketing in U.S. through February 19, 2025	n/a
Epoetin alfa	Amgen v. Hospira, No. 15-839 (D. Del.)	RETACRIT (epoetin alfa-epbx) [approved & launched]	EPOGEN/ PROCRIT [litigation #1]	9/18/2015	2	September 22, 2017, Jury found infringement and awarded Amgen $70M: Hospira's post-trial motions denied	Affirmed by Fed. Cir.: March 16, 2020, rehearing denied.
Etanercept	Immunex v. Sandoz. No 16-01118 (D.N.J.)	ERELZI (etanercept- szzs) [approved, not yet launched]	ENBREL [litigation #1]	2/26/2016	5	August 9, 2019, Judgment of infringement and no invalidity in favor of Immunex.	July 1, 2020, Affirmed by Fed. Cir.
Etanercept	Immunex v. Samsung Bioepis, No. 19-11755 (D.N.J.)	ETICOVO (etanercept- ykro) [approved, not launched]	ENBREL [litigation #2]	4/29/2019	5	November 3, 2021, Final Judgment and Order of Permanent Injunction against Samsung	n/a
Filgrastim	Amgen v. Apotex, No. 15-62081 (S.D. Fla.) [consolidated with Amgen v. Sandoz, below)	GRASTOFIL (filgrastim biosimilar) [not approved]	NEUPOGEN [litigation #2]	10/2/2015	2	November 15, 2019, Settled	n/a
Filgrastim	Amgen v. Kashiv (formerly Adello), No. 18-3347 (D.N.J.)	TPI G-CSF (filgrastim biosimilar) [not approved]	NEUPOGEN [litigation #3]	3/8/2018	17 (3)	November 25, 2019, Settled	n/a

Reference Product (RP) Proper Name	Litigation	Biosimilar (proper name) [status]	Reference Product Name	Date Litigation Filed	Number of Patents Asserted	District Court Outcome	Appellate Court Outcome
Filgrastim	Amgen v. Hospira, Nos. 18-1064, 20-561 (D. Del.)	NIVESTYM (filgrastim-aafi) [approved & launched]	NEUPOGEN [litigation #4]	7/18/2018	1 (2)	September 8, 2021, Settled	n/a
Filgrastim	Amgen v. Sandoz, No. 14-474 (N.D. Cal.) [consolidated with Amgen v. Apotex, above)]	ZARXIO (filgrastim- sndz) [approved & launched]	NEUPOGEN [litigation #1]	10/24/2014	1	March 19, 2015, Summary judgment of non-infringement in favor of Sandoz.	May 8, 2019. Affirmed by Fed. Cir.: Opinion modified on panel rehearing.
Filgrastim	Amgen v. Tanvex, No. 19-1374 (S.D. Cal.)	TX-01 (filgrastim biosimilar) [not approved]	NEUPOGEN [litigation #5]	7/23/2019	1	Settled	n/a
Infliximab	Janssen v. Celltrion, No. 17-11008 (D Mass.)	INFLECTRA (infliximab-dyyb) [approved & launched]	REMICADE [litigation #1]	3/6/2015 (refiled 5/31/2017)	2	July 30, 2018, Summary judgment of invalidity as to '471 patent. Summary judgment of non-infringement as to '083 patent, subject to any appeal	March 5, 2020. Fed. Cir. Appeal of '471 judgment dismissed; '083 judgment affirmed, both in favor of Celltrion.
Infliximab	Janssen v. Samsung Bioepis, No. 17-3524 (D.N.J.)	RENFLEXIS (infliximab-abda) [approved & launched]	REMICADE [litigation #2]	5/17/2017	3	November 30, 2017, Parties agreed to Voluntary Dismissal with prejudice.	n/a
Natalizumab	Biogen Inc. et al. v. Sandoz Inc. et al. No. 1:22-cv-1190 (D. Del.)	TYRUKO (natalizumab-sztn) [approved, not yet launched]	TYSABRI	9/19/2022	6	June 20, 2023, Preliminary injunction against Sandoz denied; trial scheduled for May 5, 2025; May 2024; settled. July 12, 2024, Claim construction order	n/a
Pegfilgrastim	Amgen v. Hospira & Pfizer No. 20-201 P. Del.)	NYVEPRIA (pegfilgrastim-apgf) [approved & launched]	NEULASTA [litigation #5]	2/11/2020	1	March 21, 2022, Settled	
Pegfilgrastim	Amgen v. Apotex, No. 15-61631 (S.D. Fla.) [consolidated with #5 below]	LAPELGA (pegfilgrastim biosimilar) [not approved]	NEULASTA [litigation #1]	8/6/2015	3	November 15, 2019, Settled	n/a
Pegfilgrastim	Amgen v. Sandoz, No. 16-2581 (N.D. Cal.) [consolidated with #1 above]	ZIEXTENZO (pegfilgrastim-bmez) [approved & launched]	NEULASTA [litigation #2]	3/4/2016		December 19, 2017, Summary judgment of non-infringement in favor of Sandoz	May 8, 2019. Affirmed by Fed. Cir.: opinion modified on panel rehearing

Reference Product (RP) Proper Name	Litigation	Biosimilar (proper name) [status]	Reference Product Name	Date Litigation Filed	Number of Patents Asserted	District Court Outcome	Appellate Court Outcome
Pegfilgrastim	Amgen v. Accord (previously Apotex). No. 18-61828 (S.D. Fla.) [follow-on case]	LAPELGA (pegfilgrastim biosimilar) [not approved]; GRASTOFIL (filgrastim biosimilar) [not approved]	NEULASTA [litigation #1]; NEUPOGEN [litigation #2]	8/7/2018		November 15, 2019, Settled	n/a
Pegfilgrastim	Amgen v. Coherus. No. 17-546 (D. Del.)	UDENYCA (pegfilgrastim-cbqv) [approved & launched]	NEULASTA [litigation #3]	5/10/2017	1	March 27, 2018, Motion by Coherus to dismiss case granted.	April 19, 2023. Dismissal affirmed by Fed. Cir.
Pegfilgrastim	Amgen v. Mylan. No. 17-1235 (W.D. Pa.)	FULPHILA (pegfilgrastim-jmdb) [approved & launched]	NEULASTA [litigation #4]	9/22/2017	2	May 9, 2019, Stipulation of non-infringement	September 17, 2019. Fed. Cir. Endorses stipulation and order of non-infringement of patent '997.
Rituximab	Genentech v. Sandoz. No. 17-13507 (D.N.J.)	GP2013 (rituximab biosimilar) [not approved]	RITUXAN [litigation #1]	12/21/2017	24	December 6, 2018, Settled	n/a
Rituximab	Genentech v. Celltrion, Nos.18-574. -11553 (D. N. J.)	TRUXIMA (nhiximab- abbs) [approved & launched]	RITUXAN [litigation #2]	1/12/2018	40	November 1, 2018, Settled	n/a
Tocilizumab	Genentech, et al. v. Biogen MA and Bio-Thera Solutions 1:23-cv-11573 (D. Ma.)	TOFIDENCE (tocilizumab-bavi) [approved and launched]	ACTEMRA	7/13/2023		October 23, 2023, Settled	n/a
Trastuzumab	Genentech v. Pfizer. No. 17-1672 (D. Del.)	TRAZIMERA (trastuzumab-qyyp) [approved & launched]	HERCEPTIN [litigation #1]	11/17/2017	21	December 4, 2018, Settled	n/a
Trastuzumab	Genentech v. Celltrion, Nos 18-095. -1025 (D. Del.)	HERZUMA (trastuzumab-pkrb) [approved & launched]	HERCEPTIN [litigation #2]	1/12/2018	20	December 27, 2018, Settled	n/a
Trastuzumab	Genentech v. Amgen, No. 18-924 (D. Del.)	KANJINTI (trastuzumab-anns) [approved & launched]	HERCEPTIN [litigation #3]	6/21/2018	37	July 19, 2019, Genentech's motions for a preliminary injunction and temporary restraining order were denied.	Denial of PI affirmed on interlocutory appeal
Trastuzumab	Genentech v. Samsung Bioepis, No. 18-1363 (D. Del)	ONTRUZANT (trastuzumab-dttb) [approved & launched]	HERCEPTIN [litigation #4]	9/4/2018	21	July 1, 2019, Settled	n/a

Reference Product (RP) Proper Name	Litigation	Biosimilar (proper name) [status]	Reference Product Name	Date Litigation Filed	Number of Patents Asserted	District Court Outcome	Appellate Court Outcome
Trastuzumab	Genentech, Inc. v. Tanvex Biopharma USA et al. No. 1:22-CV-0809 (S.D. Cal.)	TX05 (trastuzumab) [not approved]	HERCEPTIN [litigation #5]	6/2/2022	3	February 1, 2023, Settled	n/a
Ustekinumab	Janssen Biotech, Inc. v. Amgen Inc., No. 1:22-cv-0 1549 (D. Del.)	WEZLANA (ustekinumab-auub) [approved, not yet launched]	STELARA	11/29/2022	6	May 22, 2023, Settled, to launch January 1, 2025	n/a

n/a = not applicable
PI = permanent injunction
TRO = temporary restraining order
Sources: Goodwin, 2024. Big Molecule Watch. https://www.bigmoleculewatch.com/bpcia-patent-litigations/

6.1.2.6 Impact of Reducing the Litigation Burden Associated with Patent Thickets

As discussed in the previous section, patent thickets often serve as a protective barrier for RP manufacturers, prolonging their market exclusivity. Therefore, reducing patent thickets around an RP can enhance the ability of biosimilar competitors to enter the market more swiftly by simplifying the complex patent challenges that typically delay market launch. Challenging numerous patents and engaging in lengthy litigation can be prohibitively expensive for biosimilar developers, especially small biosimilar developers. Putting aside the cost of litigation, even the resources required for discovery whereby a biosimilar company determines which patents are applicable to a given RP, may have a deterrent effect on small potential biosimilar entrants. Reducing the number of patents in a thicket decreases the legal burden and associated costs, making it more financially viable for developers to invest in biosimilar development. Additionally, listing these patents in the Purple Book (similar to Orange Book patent listings for small molecule drugs) is likely to reduce upfront discovery costs. A decrease in the litigation burden associated with these thickets (estimated to average $16 million in our model per biosimilar) in return can improve the ENPV of a developer improving the likelihood of market entry.

Table 41, Table 42, and Table 43 present the results of scenarios for biosimilar markets less than $500 million per year, between $500 million and $1 billion per year, and greater than $1 billion per year, respectively, in which we ran with the analytical model to determine the impact of reducing the litigation burden of patent thickets on biosimilars. Regardless of the market size, the total average development cost decreases by $16 million, which corresponds to our estimated litigation burden associated with patent thickets. Additionally, regardless of the market size, the total expected drug development duration decreases by about two years. Removing the patent litigation barrier increases the ENPV of biosimilars by $74.3 million for markets greater than $1 billion (Table 43), by $76.2 million for markets greater than $500 million but less than $1 billion (Table 42), and by $72 million for markets less than $500 million (Table 41).

Table 41. Estimated Impact on Biosimilars of Reducing the Litigation Burden of Patent Thickets Given an RP Market of Less Than $500 Million per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Yes			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline Patent Litigation	Change Scenario No Patent Litigation	Difference
Total Cost ($ Million)	All	$130.97 ($85.2, $212.3)	$114.97 ($69.2, $196.3)	-12.9% (-18.8%, -7.5%)

Total Expected Cost ($ Million)		$188.67 ($111.5, $302.7)	$172.67 ($95.5, $286.7)	-9.1% (-14.3%, -5.3%)
Total Capitalized Cost ($ Million)		$205.83 ($122.7, $328.8)	$150.21 ($79.5, $254.9)	-28.0% (-35.2%, -22.5%)
Total Expected Capitalized Cost ($ Million)		$313.78 ($167.0, $480.5)	$242.09 ($117.2, $384.0)	-23.7% (-29.8%, -20.1%)
Total Expected Drug Development Duration (Years)		10.5 (8.6, 12.7)	8.5 (6.6, 10.8)	-19.0% (-23.3%, -15.0%)
Total Expected Lifetime Revenues (Million $)	1	$309.49 ($0.7, $1,214.5)		
	2	$204.20 ($0.5, $801.3)		
	3	$107.64 ($0.3, $422.4)		No Change
	4 or 5	$52.95 ($0.1, $207.8)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$280.26 ($0.7, $1,099.8)		
	2	$183.19 ($0.4, $718.9)		
	3	$96.32 ($0.2, $378.0)		No Change
	4 or 5	$47.26 ($0.1, $185.5)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	-$33.51 (-$424.0, $762.2)	$38.18 (-$335.5, $832.4)	68.3% (9.3%, 490.2%)
	2	-$130.58 (-$426.8, $412.7)	-$58.89 (-$336.6, $479.2)	85.8% (18.0%, 483.8%)
	3	-$217.45 (-$432.3, $63.6)	-$145.76 (-$342.1, $130.4)	80.1% (20.8%, 318.2%)
	4 or 5	-$266.51 (-$463.6, -$101.3)	-$194.82 (-$359.0, -$37.7)	33.9% (20.7%, 62.5%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 42. Estimated Impact on Biosimilars of Reducing the Litigation Burden of Patent Thickets Given an RP Market Greater Than $500 Million but Less Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Yes			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable		Baseline	Change Scenario	Difference

	Biosimilar Entry Order	Patent Litigation	No Patent Litigation	
Total Cost ($ Million)	All	$142.24 ($85.2, $212.3)	$126.24 ($69.2, $196.3)	-12.0% (-18.8%, -7.5%)
Total Expected Cost ($ Million)		$206.70 ($111.5, $302.7)	$190.70 ($95.5, $286.7)	-8.4% (-14.3%, -5.3%)
Total Capitalized Cost ($ Million)		$224.29 ($122.7, $328.8)	$165.93 ($79.5, $254.9)	-27.0% (-35.2%, -22.5%)
Total Expected Capitalized Cost ($ Million)		$344.30 ($167.0, $480.5)	$268.07 ($117.2, $384.0)	-22.9% (-29.8%, -20.1%)
Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)	8.6 (6.6, 10.8)	-18.9% (-23.3%, -15.0%)
Total Expected Lifetime Revenues (Million $)	1	$2,001.37 ($1,456.6, $2,622.5)		No Change
	2	$1,320.47 ($961.1, $1,730.3)		
	3	$696.05 ($506.6, $912.1)		
	4 or 5	$342.39 ($249.2, $448.7)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$1,812.36 ($1,319.1, $2,374.8)		No Change
	2	$1,184.65 ($862.2, $1,552.3)		
	3	$622.87 ($453.3, $816.2)		
	4 or 5	$305.63 ($222.4, $400.5)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	$1,468.07 ($868.0, $2,124.3)	$1,544.29 ($960.1, $2,184.2)	5.7% (2.6%, 10.6%)
	2	$840.36 ($411.1, $1,307.2)	$916.58 ($503.2, $1,367.1)	10.6% (4.1%, 22.6%)
	3	$278.58 ($2.3, $574.4)	$354.80 ($94.4, $635.3)	64.6% (9.0%, 319.5%)
	4 or 5	-$38.66 (-$228.6, $188.3)	$37.56 (-$136.5, $238.1)	386.2% (26.6%, 2964.8%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 43. Estimated Impact on Biosimilars of Reducing the Litigation Burden of Patent Thickets Given an RP Market Greater Than $1 Billion per Year Prior to Biosimilar Entry

Parameters	
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)
Location of PK/PD similarity Study	40% US and 60% EU
Bridging Study Needed?	Yes
CES Needed?	Yes
Location of CES	40% US and 60% EU
Switching Study Needed?	No
Device Development Needed?	No
PAI Needed?	Yes

Parameters				
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline Patent Litigation	Change Scenario No Patent Litigation	Difference
Total Cost ($ Million)	All	$135.35 ($90.1, $206.2)	$119.35 ($74.1, $190.2)	-12.2% (-17.8%, -8.0%)
Total Expected Cost ($ Million)		$199.24 ($118.3, $304.6)	$183.24 ($102.3, $288.6)	-8.3% (-13.5%, -5.4%)
Total Capitalized Cost ($ Million)		$212.18 ($130.5, $329.1)	$155.64 ($86.1, $255.2)	-27.2% (-34.0%, -22.6%)
Total Expected Capitalized Cost ($ Million)		$331.59 ($177.6, $508.0)	$257.27 ($126.2, $407.4)	-22.9% (-28.9%, -19.9%)
Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)	8.7 (6.6, 10.8)	-18.8% (-23.3%, -15.0%)
Total Expected Lifetime Revenues (Million $)	1	$10,847.78 ($3,127.5, $44,624.4)		No Change
	2	$7,157.17 ($2,063.5, $29,442.4)		
	3	$3,772.73 ($1,087.7, $15,519.9)		
	4 or 5	$1,855.82 ($535.1, $7,634.3)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$9,823.32 ($2,832.1, $40,410.1)		No Change
	2	$6,421.03 ($1,851.2, $26,414.1)		
	3	$3,376.09 ($973.4, $13,888.2)		
	4 or 5	$1,656.58 ($477.6, $6,814.7)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	$9,491.73 ($2,543.7, $40,002.8)	$9,566.05 ($2,611.6, $40,088.4)	1.4% (0.2%, 2.7%)
	2	$6,089.43 ($1,562.8, $26,006.8)	$6,163.76 ($1,630.7, $26,092.4)	2.2% (0.3%, 4.4%)
	3	$3,044.50 ($699.2, $13,480.9)	$3,118.82 ($759.5, $13,566.5)	4.8% (0.6%, 10.2%)
	4 or 5	$1,324.99 ($202.9, $6,407.4)	$1,399.31 ($276.2, $6,493.0)	15.0% (1.3%, 41.1%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

6.1.3 Comparative Efficacy Studies (CESs)

Once a proposed biosimilar emerges from preclinical bioassays and in vitro testing, its pharmaco-dynamics and -kinetics (PK/PD) will be assessed in PK/PD similarity studies using samples of 20 to 80 healthy volunteers. For biosimilars, these studies will often be used to compare the biosimilar and RP's effect on the body and how closely they match in their systemic exposure and on biomarkers, if applicable. CESs for biosimilars usually compare the proposed biosimilar with the RP to determine how close the two are in their clinical effect, adverse event profile, and immunogenicity. In order to obtain statistically meaningful results,

CESs usually require several hundred subjects drawn from patient populations. They also take place over several months to a year depending on the clinical effects being measured and to potentially identify side effects or adverse events [116].

6.1.3.1 Comparative Efficacy Studies (CESs) as a Barrier for Biosimilar Development

When the BPCIA was enacted in 2010, biosimilars were regulated via a similar, though abbreviated, approval pathway to that used for RPs, i.e., analytical characterization followed by animal experimentation, if needed, then PK and/or PD studies, and culminating in CESs [117]. When this regulatory pathway was established for biosimilars, one of the main goals was to identify potential differences in immunogenicity between the biosimilar and the RP [118]. However, since then no differences in safety, efficacy, or immunogenicity have been reported between biosimilars and their RPs [119, 117]. Indeed, several recent studies concluded that CESs for biosimilars do not provide useful information about the safety and efficacy of the drugs for regulatory purposes, especially when information has been gleaned from in vitro comparisons of the biosimilar and the RP and PK/PD similarity studies [120, 24, 121].

Do CESs Properly Address Immunogenicity Concerns?

Cassie Ramel, PharmD, BCPS, a clinical pharmacist at Mayo Clinic, said at the Academy of Managed Care Pharmacy 2024 annual meeting, “it takes large patient populations to even see them [adverse events], so if we’re only performing clinical studies in a few hundred patients, are we really capturing these events? Or are we kind of doing these clinical studies, having the additional costs, without giving us that additional supportive information” [122]? Some experts assert that CESs for biosimilars are not scientifically valid because they do not provide useful regulatory information, and if they are not scientifically valid, they are also not ethically valid [123]. Currently, FDA can waive clinical studies that are determined to be unnecessary if the safety and efficacy of a biosimilar is already established based on analytical comparability to the RP and PK/PD similarity studies [124, 123]. CESs are more costly than PK/PD similarity studies [125], and they pose a considerable time commitment and challenges with patient recruitment. For these reasons, the requirement to conduct CESs is facing scrutiny [123].

Cost of CESs

Biosimilar development is expensive, with approximately $100 million to $300 million in costs reported per biosimilar development project, and clinical studies account for more than half of total costs [126]. Ledesma [125], estimated that CESs have average costs of $20 million, whereas PK/PD similarity and II clinical studies average $4 million and $13 million respectively [125]. Per patient, CESs cost a median of $41,117 [125]. Specifically, CESs require that biosimilar sponsors obtain substantial quantities of the RP (often thousands of doses) to administer to the patient group receiving the reference treatment, which can be a difficult process [127]. Some RPs cost thousands of dollars per dose and are administered multiple times to several hundred patients over the course of a single study. The total cost of the RP for use in studies can often add millions of dollars to the overall CES costs. Hence, the cost of a CES largely depends on the number of subjects.

Table 44 presents the total number of CESs and the sample sizes of FDA CESs for biosimilars that have been approved. The majority of biosimilars have one or two CESs, with the highest number of CESs reported for Inflectra and Actemra at seven studies each. The cost of a CES also depends on the therapeutic area, among other considerations such as the number of clinical sites, drug type, specific treatment protocols, and study locations. For example, prior research has shown that pain and anesthesia CESs are the costliest at $52.9 million per study, followed by ophthalmology ($30.7 million) and cardiovascular ($25.2 million) CESs [128].

Table 44. Number and Sample Sizes of CESs of FDA-Approved Biosimilars

Biosimilar Name	Proper Name	Number of CESs [a]	Sample Size of FDA CESs
Avsola	infliximab-axxq	1	558
Zarxio	filgrastim-sndz	2	204 170
Renflexis	infliximab-abda	1	584
Inflectra	infliximab-dyyb	7	109 606 15
Tyruko	natalizumab-sztn	1	265
Ziextenzo	pegfilgrastim-bmez	2	308 316
Tofidence	tocilizumab-bavi	1	621
Eticovo	etanercept-ykro	1	596
Nivestym	filgrastim-aafi	1	n/a
Ixifi	infliximab-qbtx	1	650
Semglee	insulin glargine-yfgn	6	127 558 560 219
Rezvoglar	insulin glargine-aglr	5	n/a
Fulphila	pegfilgrastim-jmdb	1	194
Cimerli	ranibizumab-eqrn	1	477
Byooviz	ranibizumab-nuna	1	705
Truxima	rituximab-abbs	3	257 372 140
Riabni	rituximab-arrx	2	311 256
Ruxience	rituximab-pvvr	1	394
Actemra	tocilizumab-aazg	7	188 112
Kanjinti	trastuzumab-anns	1	725
Ogivri	trastuzumab-dkst	1	493
Ontruzant	trastuzumab-dttb	1	875
Herzuma	trastuzumab-pkrb	2	562
Trazimera	trastuzumab-qyyp	2	707
Yusimry	adalimumab-aqvh	1	545
Hyrimoz	adalimumab-adaz	2	465
Idacio	adalimumab-aacf	1	441
Yuflyma	adalimumab-aaty	3	648 62

Biosimilar Name	Proper Name	Number of CESs [a]	Sample Size of FDA CESs
Cyltezo	adalimumab-adbm	4	645
Abrilada	adalimumab-afzb	2	597
Amjevita	adalimumab-atto	4	526 350
Hadlima	adalimumab-bwwd	1	544
Hulio	adalimumab-fkjp	1	730
Vegzelma	bevacizumab-adcd	1	689
Mvasi	bevacizumab-awwb	2	642
Zirabev	bevacizumab-bvzr	2	710
Alymsys	bevacizumab-maly	1	627
Retacrit	epoetin alfa-epbx	2	612 320
Erelzi	etanercept-szzs	2	531

n/a = not applicable; there have been no FDA CESs for the indicated biosimilar
[a] In cases when the number of CESs does not match the number of reported sample sizes, the number of CESs also includes non-FDA studies such as EMA studies.

Time Challenges of CESs

Overall, the development process may be as long as five to nine years total for a typical biosimilar [122]. The median length of time for biosimilar CESs is 52 weeks, or one year [129]. Other researchers have estimated the average CES duration for biosimilars at 22 months [130]. In addition to this patient follow-up time, there are other time requirements for CESs not included in this estimate, including the time required to design the study, time for obtaining necessary approvals, and time for recruiting patients into the study [131]. After the data analysis and results publication processes are factored in, the total time commitment for CESs exceeds the above estimates.

Patient Recruitment Challenges of CESs

Another challenge in conducting CESs for biosimilars is the difficulty in recruiting and retaining patients, which can cause delays in development timelines. Patient recruitment is time consuming and has been reported to constitute 30% of clinical timelines [132]. Investigators design CESs in such a way that one group of patients receives standard treatment, such as the RP, and another group receives the biosimilar treatment. Patients may balk at study participation if they know there is a chance they will receive a biosimilar treatment that may or may not work compared to an approved RP. This is especially true for CESs of treatments for serious diseases such as cancer [127]. Therefore, appropriate education of clinical study staff, physicians, and patients is crucial for enhancing CES patient recruitment [132]. Another strategy for meeting patient recruitment goals for CESs of biosimilars is to conduct the studies in markets that have the greatest unmet need for the RP [132]. Patients may be incentivized to participate if they do not otherwise have access to the RP. Additionally, multiple CESs may be recruiting patients with the same clinical conditions at the same time, causing competition and potential delays in recruitment for biosimilar studies.

6.1.3.2 Impact of Removing CES

Table 45, Table 46, and Table 47 present the results of scenarios for biosimilar markets less than $500 million per year, between $500 million and $1 billion per year, and greater than

$1 billion per year, respectively, in which we ran the analytical model to determine the impact of removing the CES on biosimilars. The total average development cost decreases by 23% for biosimilar markets greater than $1 billion per year and decreases by 25% for biosimilar markets less than $1 billion per year when the CES is removed. Additionally, regardless of the market size, the total expected drug development duration decreases by about two years. Regardless of entry order, removing the CES increases the ENPV of biosimilars by $112 million for markets greater than $1 billion (Table 47), by $124 million for markets greater than $500 million but less than $1 billion (Table 46), and by $113 million for markets less than $500 million (Table 45).

Table 45. Estimated Impact on Biosimilars of Removing the CES Given an RP Market of Less Than $500 Million per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Depends on scenario			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline CES	Change Scenario No CES	Difference
Total Cost ($ Million)	All	$130.97 ($85.2, $212.3)	$98.15 ($61.0, $151.1)	-25.0% (-30.5%, -19.3%)
Total Expected Cost ($ Million)		$188.67 ($111.5, $302.7)	$136.47 ($76.0, $203.2)	-27.7% (-33.9%, -21.7%)
Total Capitalized Cost ($ Million)		$205.83 ($122.7, $328.8)	$138.12 ($79.6, $210.7)	-32.6% (-39.2%, -26.1%)
Total Expected Capitalized Cost ($ Million)		$313.78 ($167.0, $480.5)	$200.55 ($102.2, $288.7)	-35.8% (-42.6%, -29.2%)
Total Expected Drug Development Duration (Years)		10.5 (8.6, 12.7)	8.4 (6.9, 9.9)	-19.4% (-23.3%, -16.8%)
Total Expected Lifetime Revenues (Million $)	1	$309.49 ($0.7, $1,214.5)		No Change
	2	$204.20 ($0.5, $801.3)		
	3	$107.64 ($0.3, $422.4)		
	4 or 5	$52.95 ($0.1, $207.8)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$280.26 ($0.7, $1,099.8)		No Change
	2	$183.19 ($0.4, $718.9)		
	3	$96.32 ($0.2, $378.0)		

	4 or 5		$47.26 ($0.1, $185.5)	
ENPV over Biosimilar Product's Lifetime (Million $)	1	-$33.51 (-$424.0, $762.2)	$79.72 (-$257.4, $899.5)	109.7% (11.8%, 690.4%)
	2	-$130.58 (-$426.8, $412.7)	-$17.35 (-$258.9, $510.2)	122.3% (23.0%, 761.7%)
	3	-$217.45 (-$432.3, $63.6)	-$104.23 (-$260.4, $181.7)	113.8% (29.5%, 486.0%)
	4 or 5	-$266.51 (-$463.6, -$101.3)	-$153.29 (-$263.5, -$15.4)	50.1% (29.3%, 84.7%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 46. Estimated Impact on Biosimilars of Removing the CES Given an RP Market Greater Than $500 Million but Less Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Depends on scenario			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline CES	Change Scenario No CES	Difference
Total Cost ($ Million)	All	$142.24 ($85.2, $212.3)	$106.66 ($61.0, $151.1)	-24.7% (-30.4%, -19.3%)
Total Expected Cost ($ Million)		$206.70 ($111.5, $302.7)	$149.43 ($76.0, $203.2)	-27.4% (-33.2%, -21.7%)
Total Capitalized Cost ($ Million)		$224.29 ($122.7, $328.8)	$150.68 ($79.6, $210.7)	-32.3% (-39.2%, -26.1%)
Total Expected Capitalized Cost ($ Million)		$344.30 ($167.0, $480.5)	$220.18 ($102.2, $288.7)	-35.6% (-42.6%, -29.2%)
Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)	8.5 (6.9, 9.9)	-19.1% (-23.3%, -16.8%)
Total Expected Lifetime Revenues (Million $)	1	$2,001.37 ($1,456.6, $2,622.5)		No Change
	2	$1,320.47 ($961.1, $1,730.3)		
	3	$696.05 ($506.6, $912.1)		
	4 or 5	$342.39 ($249.2, $448.7)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$1,812.36 ($1,319.1, $2,374.8)		No Change
	2	$1,184.65 ($862.2, $1,552.3)		

	3		$622.87 ($453.3, $816.2)	
	4 or 5		$305.63 ($222.4, $400.5)	
ENPV over Biosimilar Product's Lifetime (Million $)	1	$1,468.07 ($868.0, $2,124.3)	$1,592.18 ($1,045.9, $2,203.4)	9.5% (3.3%, 20.6%)
	2	$840.36 ($411.1, $1,307.2)	$964.47 ($589.0, $1,386.3)	17.8% (5.4%, 43.7%)
	3	$278.58 ($2.3, $574.4)	$402.69 ($180.1, $655.0)	117.4% (11.7%, 617.6%)
	4 or 5	-$38.66 (-$228.6, $188.3)	$85.45 (-$50.8, $253.1)	530.2% (34.6%, 3939.1%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 47. Estimated Impact on Biosimilars of Removing the CES Given an RP Market Greater Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Depends on scenario			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline CES	Change Scenario No CES	Difference
Total Cost ($ Million)	All	$135.35 ($90.1, $206.2)	$104.17 ($62.6, $151.8)	-22.9% (-30.5%, -19.2%)
Total Expected Cost ($ Million)		$199.24 ($118.3, $304.6)	$148.62 ($78.1, $214.5)	-25.3% (-33.9%, -21.6%)
Total Capitalized Cost ($ Million)		$212.18 ($130.5, $329.1)	$146.99 ($81.8, $216.9)	-30.3% (-37.3%, -26.0%)
Total Expected Capitalized Cost ($ Million)		$331.59 ($177.6, $508.0)	$219.55 ($105.3, $317.0)	-33.4% (-40.7%, -29.2%)
Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)	8.7 (6.9, 9.9)	-18.4% (-22.0%, -16.8%)
Total Expected Lifetime Revenues (Million $)	1	$10,847.78 ($3,127.5, $44,624.4)		No Change
	2	$7,157.17 ($2,063.5, $29,442.4)		
	3	$3,772.73 ($1,087.7, $15,519.9)		
	4 or 5	$1,855.82 ($535.1, $7,634.3)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$9,823.32 ($2,832.1, $40,410.1)		No Change
	2	$6,421.03		

		($1,851.2, $26,414.1)		
	3	$3,376.09 ($973.4, $13,888.2)		
	4 or 5	$1,656.58 ($477.6, $6,814.7)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	$9,491.73 ($2,543.7, $40,002.8)	$9,603.77 ($2,629.3, $40,157.6)	2.1% (0.3%, 4.9%)
	2	$6,089.43 ($1,562.8, $26,006.8)	$6,201.47 ($1,648.3, $26,161.6)	3.3% (0.5%, 8.1%)
	3	$3,044.50 ($699.2, $13,480.9)	$3,156.54 ($775.7, $13,635.7)	7.2% (1.0%, 18.8%)
	4 or 5	$1,324.99 ($202.9, $6,407.4)	$1,437.03 ($294.2, $6,562.2)	22.9% (2.2%, 77.0%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

6.2 Incentives

The prodigious dollar value of many biologic markets hardly needs to be mentioned as the primary incentive for companies to take on the expense and risks of developing a biosimilar and competing with the RP and other potential market entrants. Other potential incentives essentially comprise the countermeasures to the barriers mentioned above. Some of these measures that were mentioned by SMEs interviewed for this study include the following:

- More vigorous movement by FDA, on a case-by-case basis, toward eliminating time- and money-intensive CESs. This could take the form of developing more product specific guidances (PSGs) that are explicit regarding how a biosimilar candidate can develop pre-clinical data that could obviate the need for safety and efficacy studies.
- Increases in funding for the USPTO to hire more examiners and give more exacting scrutiny of RP patent applications.
- Continue and augment current agency and professional group efforts to bring physicians up to speed on why biosimilars are less risky than they perceive.
- Amending reimbursement procedures for Medicare (and other insurers) to encourage prescribing of the lowest cost/best value biologic product and preferred formulary placement for biosimilars in the retail setting.[45]

[45] Several policy ideas have been proposed to encourage Medicare prescribers and plans to use lower-cost or best value biologics, including biosimilars since 2016. One approach has been to increase the add-on fee for newly approved biosimilars under Medicare Part B, a temporary measure designed to make biosimilars more attractive

- Publication by FDA of more detailed PSGs directed at developers of biosimilars of specific RPs. Interviewees agreed that CDER was more than willing to meet with them when questions arose, but that such meetings often had to be scheduled several months out. PSGs would help biosimilar companies with their initial decision-making and could answer some questions that might otherwise take weeks or months to answer.

6.2.1 Automatic Interchangeability Designation

As was noted above in section 6.1.1, the interchangeable designation as defined in BPCIA, and FDA's 2019 guidance regarding the design of additional clinical switching studies needed to gain interchangeable designation, combined to form a barrier to biosimilar development and uptake. The additional time and cost of switching studies discouraged applicants from seeking the designation, while the very existence of the designation and the additional research needed to achieve it created the impression that there was a second, higher tier of biosimilars with standards that, up until 2023, very few biosimilars had achieved [133] [134] [135]. FDA's efforts to dispel this misapprehension among many prescribers and other stakeholders likely had a positive effect on biosimilar uptake, but these educative efforts undoubtedly took some time to implement and take effect [135]. Meanwhile, biosimilar uptake in the United States was falling short of expectations [136].

6.2.1.1 Automatic Interchangeability as an Incentive for Biosimilar Development

In contrast to FDA—which, under BPCIA, was responsible for assessing and approving applications for interchangeable designation—EMA, which approved its first biosimilar in 2006, initially took no position on interchangeability. Possibly, this was because policy on pharmacy substitution of generics or biosimilars for their respective RP was the province of each member state. By 2022, however, the Heads of Medicines Agency and EMA felt the need to clarify their position and issued a joint statement on interchangeability [137]. They stated unequivocally that "biosimilar medicines approved in the European Union (EU) are interchangeable with their reference medicine or with an equivalent biosimilar.... Approved biosimilars have demonstrated similar efficacy, safety and immunogenicity compared with their reference medicines, and analysis of more than one million patient-treatment years of safety data did not raise any safety concerns" [137].

The EMA statement reiterated that pharmacy substitution was the remit of the regulatory bodies of member states. It also emphasized that replacing a prescribed biologic (or biosimilar) with a biosimilar referencing the same biologic had become a common clinical

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to physicians by enhancing their reimbursement [163]. Another method involves Medicare Advantage (MA) plans, which can implement step therapy for certain Part B drugs, requiring patients to try a biosimilar first before covering a more expensive reference biologic [164]. The Centers for Medicare & Medicaid Services (CMS) has also explored value-based purchasing demonstrations—such as reference pricing or indication-based pricing—to better align payment with drug value, although the proposal faced resistance and was ultimately withdrawn [165]. In the legislative arena, various bills have suggested sharing savings from biosimilar use directly with providers or restructuring Medicare Part D to reduce out-of-pocket costs and indirectly encourage the use of lower-priced biologics. While these proposals have not been fully advanced, they reflect a growing consensus that Medicare's drug spending could be reduced by steering prescribing toward biosimilars and other high-value products.

practice, but that "Interchange should only take place after careful consideration of the approved conditions of use (i.e., consulting the most recent product information)."

EMA had always considered that its approval of a biosimilar meant that the biosimilar could be used to replace either the RP or another biosimilar referencing the same biologic. The definition of interchangeable set forth in BPCIA, and especially the additional approval criteria that FDA (or "the Secretary" as BPCIA puts it) was called upon to define operationally and set standards for, gave FDA more specific responsibility for interchangeable safety than EMA had assumed.[46] As we discussed in section 6.1.1, the switching studies that FDA recommended in its 2017 draft guidance and 2019 Guidance [138] are likely to have made biosimilar sponsors more reluctant to pursue interchangeable status, due to their cost and the probable delay in BLA submission and approval.

More recently (as also mentioned in section 6.1.1), FDA's actions have given some indication that it is inclined to move in the direction of EMA's position that an approved biosimilar's interchangeability with its RP can be assumed, without any additional clinical studies. FDA's June 2024 revised draft guidance on interchangeability [14], points out that "Since publication of the Interchangeability Guidance [in 2019] experience has shown that for the products approved as biosimilars to date, the risk in terms of safety or diminished efficacy is insignificant following single or multiple switches between a RP and a biosimilar product."[47]

During the 10 months From October 3, 2023, to August 9, 2024, FDA designated 12 biosimilars as interchangeable.[48] Seven of these 12 interchangeables were not required to submit clinical switching study data. Biosimilar candidates of four original biologic molecules—insulin glargine, ranibizumab, ustekinumab, and aflibercept—will apparently no longer need to submit switching study data to gain interchangeable designation.

Still, FDA's effort to eliminate the barriers to interchangeable designation is likely to be incremental. BPCIA has codified specific qualities that FDA must identify in a biosimilar in order to designate it interchangeable. Barring Congressional action to amend this section of BPCIA, FDA will have to continue to assess every abbreviated BLA with an eye on whether the applicant has supplied adequate data to support interchangeable designation.

Nevertheless, we have estimated the impact on a company's ENPV of eliminating the switching study requirement and the value to a biosimilar of FDA issuing a statement similar to EMA's, i.e., that an FDA-approved biosimilar is, by virtue of its approval as a biosimilar by FDA, interchangeable with its RP and with other biosimilars referencing the same biologic.

[46] "From a scientific viewpoint, interchangeability of approved biosimilars has always been considered acceptable and did not raise any concern (1). However, EMA has to date not issued any recommendation on interchangeability. At present the EU medicines regulatory network has identified the need to explicitly state that from a scientific point of view, biosimilars approved in the EU can be considered interchangeable."

[47] FDA also pointed out that when it issued its 2019 Guidance on interchangeability, it had not received or reviewed any BLA seeking interchangeable designation and that since then their views on the topic had "evolved."

[48] Two of the 12 are provisional designations, pending resolution of market exclusivity of the first interchangeable in their markets.

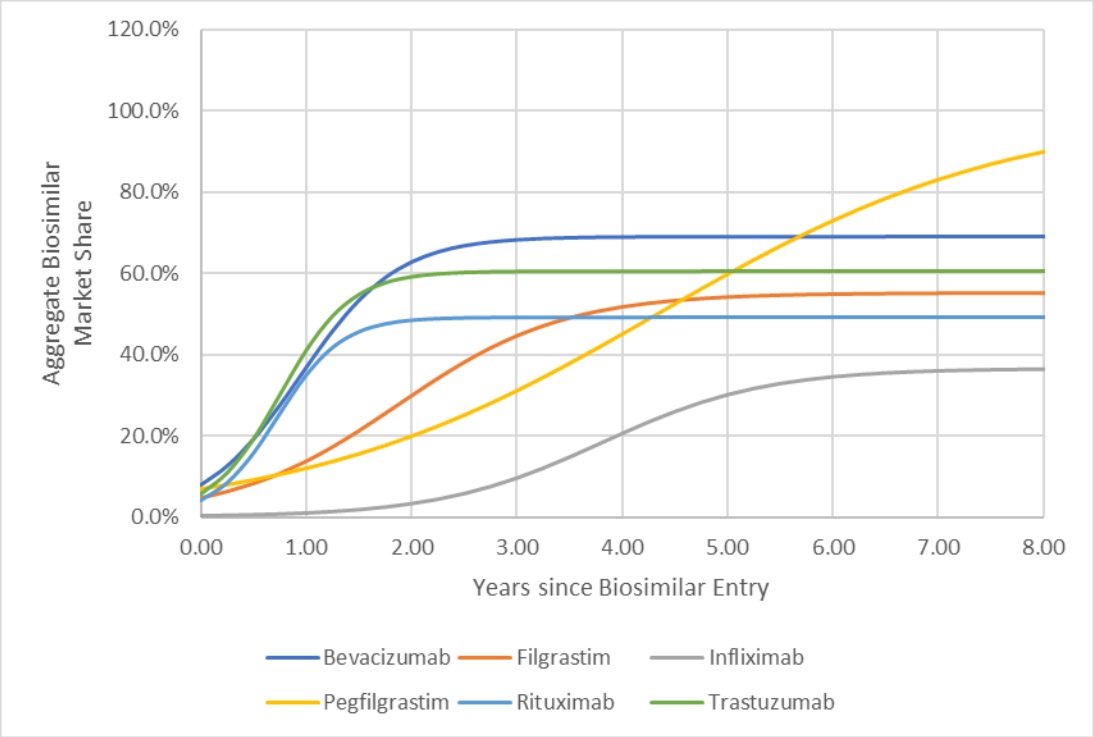
6.2.1.2 Estimating the Value of Designating all FDA-approved Biosimilars as Interchangeable

Our base model assumes that achieving interchangeability status yields no additional benefit to a biosimilar product's lifetime revenues. This is largely due to lack of data; there are only two biologic markets with biosimilar competition sold through retail pharmacies—Lantus (insulin glargine) and Humira (adalimumab)—and neither of these markets had sufficient data as of the time of our analysis. We therefore lack biosimilar data for assessing the benefit of automatic pharmacy substitution that interchangeable biosimilars receive in a retail setting. Even for physician-administered biosimilars reimbursed by medical benefits, there were no examples of interchangeables with a long enough time series to model at the time of our analysis.

Small molecule generic drugs, however, have ample data and display many characteristics of successful market uptake. Generic drugs are more often viewed as being perfect substitutes of the brand name drug. They have experienced wider acceptance than biosimilars, which has led to faster market share uptake, on average. Based on research by Rome et al., we estimate that generic drugs, in the aggregate, reach a stable market share at 30 months or 2.5 years after launch of the first generic [139].

This 30-month period is very close to the time it took for the three most successful biosimilar markets we observed—bevacizumab, rituximab, and trastuzumab—to reach peak market share, according to our model (see Figure 10). In all three of these markets, biosimilar products launched in 2019 or later. The other three markets we modeled—filgrastim, pegfilgrastim, and infliximab—had biosimilars that launched in 2015 to 2018 and slower market uptake, possibly due to more hesitation by physicians and patients when biosimilars were initially being marketed in the United States.

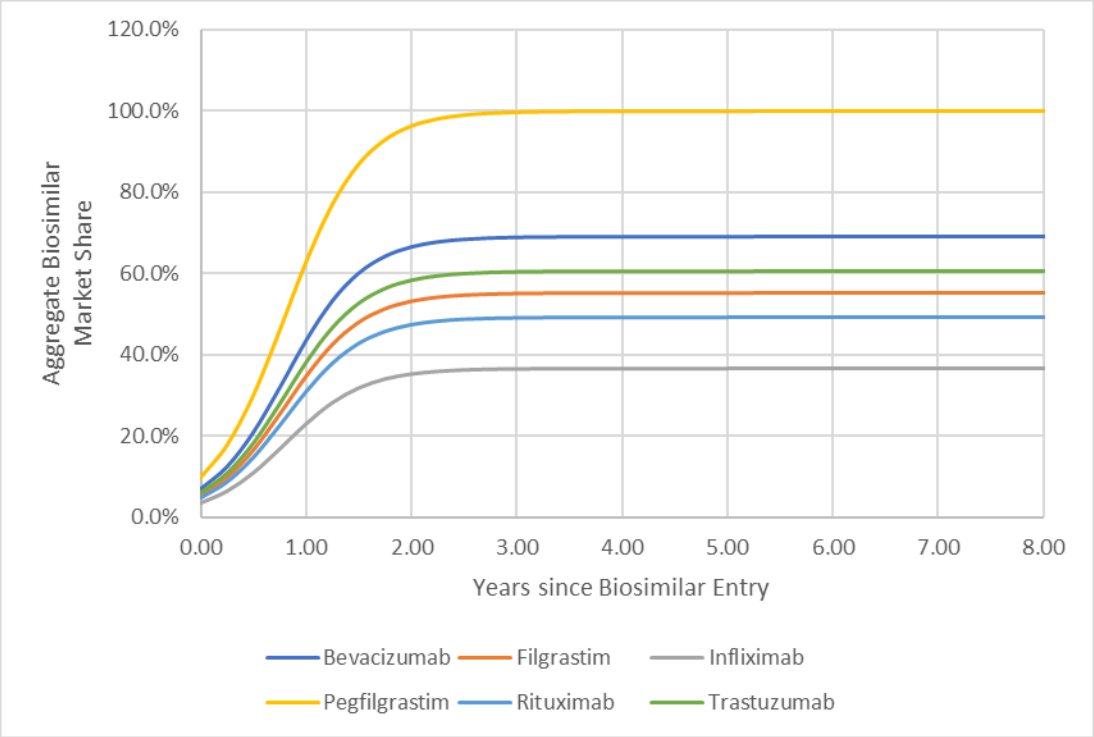
Figure 10. Biosimilar Market Share Uptake Curves: Baseline Scenario



The discrepancy between these two groups of biosimilars suggests that higher patient and physician acceptance likely benefits all biosimilars, including physician-administered drugs that are not dispensed in a retail pharmacy. Automatically designating all biosimilars as interchangeable would contribute to this broader acceptance. To model the increase in biosimilar revenue associated with automatic interchangeability, we therefore assumed all future biosimilars would have market share functions that increase at the same rate observed in generic drug markets and in the more successful biosimilar markets. This may be overestimating the impact of interchangeability on expected revenues. Two parameters in our biosimilar market share model control the timing and rate of the growth—the growth midpoint and the slope parameter. For each of these parameters, we calculated the average value in the more successful biosimilar markets, bevacizumab, rituximab, and infliximab.[49] We then applied these averages to all six markets and generated new estimates of revenue and ENPV based on the more optimistic biosimilar adoption scenario. This led to the modified biosimilar market share uptake curves shown below in Figure 11. Under this scenario, each biosimilar market still reaches the same final market share, but in all cases, the biosimilars have achieved 98 percent of their long-run market share by 2.5 years after the first biosimilar was launched.

[49] Among the six markets, bevacizumab, rituximab, and infliximab with the fastest uptake were also the most recent and were all oncology products. Thus, their performance might be attributable to changes in attitudes toward biosimilars, and the fact that it is easier to get new patients on the biosimilar than to convince existing patients to switch from the RP.

Figure 11. Biosimilar Market Share Uptake Curves: Automatic Interchangeability



When estimating the benefits of automatic interchangeability, we assumed there was no switching study during development—both in the baseline scenario and in the automatic interchangeability scenario. Most biosimilars have not performed a switching study, and this is true of the biosimilar products we modeled in the six biologic markets above. The slower average biosimilar adoption that is currently observed thus represents the status quo with no switching study, no interchangeability status, and greater overall hesitation. Therefore, to model the benefits of automatic interchangeability, we simply estimated the increase in revenues due to faster biosimilar adoption.

6.2.1.3 Results of Automatic Interchangeability Incentive Scenario

Table 48, Table 49, and Table 50 present the results of the analyses in which we evaluated the impact of automatically designating biosimilars as interchangeable with their RP without the need for switching studies. Table 48 presents the results of this analysis given an RP market less than $500 million per year prior to biosimilar entry, Table 49 presents the results given the RP market is greater than $500 million but less than $1 billion per year, and Table 50 presents the results given the RP market is greater than $1 billion per year. Our results show that automatic interchangeability increases total expected lifetime revenues for the biosimilar by an equal percentage regardless of the market size (19 percent for the first entrant, 28 percent for the second and third entrants, and 31 percent for the fourth or fifth entrants). This would be expected in these scenarios without switching studies, as there would be no changes to total costs and uptake of the biosimilar would be faster.

Meanwhile, automatically designating biosimilars as interchangeable with their RP without the need for switching studies increases a biosimilar's ENPV across all market sizes. In the scenarios specifically in markets greater than $500 million per year, the first biosimilars to

enter the market experience smaller percentage increases in ENPV compared to the fourth or fifth entrants. For example, given a market of $1 billion or greater, the expected ENPV for the first entrant increases by 22 percent, the second entrant's ENPV increases by 32 percent, the third entrant's ENPV increases by 35 percent, and the fourth and fifth entrants' ENPVs increase by 54 percent. On the other hand, in scenarios given a market that is less than $500 million per year, the expected ENPV for biosimilars based on entry order is not uniform; the first entrant's ENPV increases by 52 percent, the second entrant's ENPV increases by 82 percent, the third entrant's ENPV increases by 73 percent, and the fourth and fifth entrants' ENPVs increase by 13 percent.

Table 48. Estimated Impact on Biosimilars of Automatic Interchangeability given an RP Market Less Than $500 Million per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Yes			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline No Switching Study, Normal Uptake	Change Scenario No Switching Study, Faster Uptake	Difference
Total Cost ($ Million)	All	$130.97 ($85.2, $212.3)		No Change
Total Expected Cost ($ Million)		$188.67 ($111.5, $302.7)		
Total Capitalized Cost ($ Million)		$205.83 ($122.7, $328.8)		
Total Expected Capitalized Cost ($ Million)		$313.78 ($167.0, $480.5)		
Total Expected Drug Development Duration (Years)		10.5 (8.6, 12.7)		
Total Expected Lifetime Revenues (Million $)	1	$309.49 ($0.7, $1,214.5)	$369.51 ($0.9, $1,450.1)	19.4% (19.4%, 19.4%)
	2	$204.20 ($0.5, $801.3)	$261.17 ($0.6, $1,024.9)	27.9% (27.9%, 27.9%)
	3	$107.64 ($0.3, $422.4)	$137.38 ($0.3, $539.1)	27.6% (27.6%, 27.6%)
	4 or 5	$52.95 ($0.1, $207.8)	$69.11 ($0.2, $271.2)	30.5% (30.5%, 30.5%)
Total Expected Lifetime Revenues, Discounted (Million $)	1	$280.26 ($0.7, $1,099.8)	$337.41 ($0.8, $1,324.1)	20.4% (20.4%, 20.4%)
	2	$183.19 ($0.4, $718.9)	$237.12 ($0.6, $930.5)	29.4% (29.4%, 29.4%)
	3	$96.32	$124.20	28.9%

		($0.2, $378.0)	($0.3, $487.4)	(28.9%, 28.9%)
	4 or 5	$47.26 ($0.1, $185.5)	$62.44 ($0.2, $245.0)	32.1% (32.1%, 32.1%)
ENPV over Biosimilar Product's Lifetime (Million $)	1	-$33.51 (-$424.0, $762.2)	$23.64 (-$423.5, $982.1)	51.9% (0.0%, 332.5%)
	2	-$130.58 (-$426.8, $412.7)	-$76.65 (-$424.1, $611.9)	81.5% (0.0%, 639.0%)
	3	-$217.45 (-$432.3, $63.6)	-$189.57 (-$430.6, $163.4)	73.4% (0.0%, 415.8%)
	4 or 5	-$266.51 (-$463.6, -$101.3)	-$251.34 (-$440.7, -$51.0)	13.0% (0.0%, 49.2%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 49. Estimated Impact on Biosimilars of Automatic Interchangeability given an RP Market Greater Than $500 Million but Less Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Yes			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline No Switching Study, Normal Uptake	Change Scenario No Switching Study, Faster Uptake	Difference
Total Cost ($ Million)	All	$142.24 ($85.2, $212.3)		No Change
Total Expected Cost ($ Million)		$206.70 ($111.5, $302.7)		
Total Capitalized Cost ($ Million)		$224.29 ($122.7, $328.8)		
Total Expected Capitalized Cost ($ Million)		$344.30 ($167.0, $480.5)		
Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)		
Total Expected Lifetime Revenues (Million $)	1	$2,001.37 ($1,456.6, $2,622.5)	$2,389.50 ($1,739.1, $3,131.1)	19.4% (19.4%, 19.4%)
	2	$1,320.47 ($961.1, $1,730.3)	$1,688.92 ($1,229.2, $2,213.1)	27.9% (27.9%, 27.9%)
	3	$696.05 ($506.6, $912.1)	$888.36 ($646.6, $1,164.1)	27.6% (27.6%, 27.6%)
	4 or 5	$342.39 ($249.2, $448.7)	$446.94 ($325.3, $585.6)	30.5% (30.5%, 30.5%)
	1	$1,812.36	$2,181.93	20.4%

Total Expected Lifetime Revenues, Discounted (Million $)		($1,319.1, $2,374.8)	($1,588.0, $2,859.1)	(20.4%, 20.4%)
	2	$1,184.65 ($862.2, $1,552.3)	$1,533.40 ($1,116.0, $2,009.3)	29.4% (29.4%, 29.4%)
	3	$622.87 ($453.3, $816.2)	$803.19 ($584.6, $1,052.5)	28.9% (28.9%, 28.9%)
	4 or 5	$305.63 ($222.4, $400.5)	$403.77 ($293.9, $529.1)	32.1% (32.1%, 32.1%)
ENPV over Biosimilar Product's Lifetime (Million $)	1	$1,468.07 ($868.0, $2,124.3)	$1,837.63 ($1,137.0, $2,605.3)	25.7% (22.2%, 31.0%)
	2	$840.36 ($411.1, $1,307.2)	$1,189.10 ($664.9, $1,761.1)	43.7% (33.5%, 62.1%)
	3	$278.58 ($2.3, $574.4)	$458.89 ($133.5, $810.6)	115.3% (37.7%, 454.6%)
	4 or 5	-$38.66 (-$228.6, $188.3)	$59.47 (-$157.2, $302.4)	534.2% (31.7%, 4113.3%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 50. Estimated Impact on Biosimilars of Automatic Interchangeability given an RP Market Greater Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Yes			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline No Switching Study, Normal Uptake	Change Scenario No Switching Study, Faster Uptake	Difference
Total Cost ($ Million)	All	$135.35 ($90.1, $206.2)		No Change
Total Expected Cost ($ Million)		$199.24 ($118.3, $304.6)		
Total Capitalized Cost ($ Million)		$212.18 ($130.5, $329.1)		
Total Expected Capitalized Cost ($ Million)		$331.59 ($177.6, $508.0)		
Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)		
Total Expected Lifetime Revenues (Million $)	1	$10,847.78 ($3,127.5, $44,624.4)	$12,951.49 ($3,734.0, $53,278.5)	19.4% (19.4%, 19.4%)
	2	$7,157.17 ($2,063.5, $29,442.4)	$9,154.24 ($2,639.2, $37,657.7)	27.9% (27.9%, 27.9%)

	3	$3,772.73 ($1,087.7, $15,519.9)	$4,815.05 ($1,388.2, $19,807.7)	27.6% (27.6%, 27.6%)
	4 or 5	$1,855.82 ($535.1, $7,634.3)	$2,422.47 ($698.4, $9,965.3)	30.5% (30.5%, 30.5%)
Total Expected Lifetime Revenues, Discounted (Million $)	1	$9,823.32 ($2,832.1, $40,410.1)	$11,826.41 ($3,409.7, $48,650.2)	20.4% (20.4%, 20.4%)
	2	$6,421.03 ($1,851.2, $26,414.1)	$8,311.29 ($2,396.2, $34,190.1)	29.4% (29.4%, 29.4%)
	3	$3,376.09 ($973.4, $13,888.2)	$4,353.41 ($1,255.1, $17,908.6)	28.9% (28.9%, 28.9%)
	4 or 5	$1,656.58 ($477.6, $6,814.7)	$2,188.50 ($631.0, $9,002.8)	32.1% (32.1%, 32.1%)
ENPV over Biosimilar Product's Lifetime (Million $)	1	$9,491.73 ($2,543.7, $40,002.8)	$11,494.82 ($3,121.2, $48,242.9)	21.6% (20.6%, 23.0%)
	2	$6,089.43 ($1,562.8, $26,006.8)	$7,979.69 ($2,107.8, $33,782.8)	32.3% (29.9%, 35.5%)
	3	$3,044.50 ($699.2, $13,480.9)	$4,021.82 ($970.4, $17,501.3)	35.1% (29.8%, 42.9%)
	4 or 5	$1,324.99 ($202.9, $6,407.4)	$1,856.91 ($369.2, $8,595.6)	53.7% (34.2%, 95.6%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

6.2.2 Establishing a Global Comparator

Bridging studies are defined as either PK/PD similarity, II, or 3 studies conducted in a new region of interest to allow extrapolation of a foreign RP's clinical data to the population in the new region [140]. Currently, bridging studies are required of biosimilar applicants if they are using a foreign-sourced RP in their various comparative studies. This is the case in the EU, Australia, Switzerland, and the United States [141]. Historically, regulators required bridging studies to ensure that the substitute, or comparator, biologic, for the RP has no meaningful clinical differences compared to the RP in the new population or region of interest.

6.2.2.1 Global Comparator as an Incentive for Biosimilar Development

In 2017, Webster and Woollett argued that bridging studies between different versions of RPs do not provide patient benefit nor significantly contribute to the scientific basis of local biosimilar regulatory applications [141]. Moreover, bridging studies are costly in terms of time, resources, and money, and therefore Webster and Woollett suggested eliminating or minimizing the bridging study requirements for biosimilar regulatory approvals [141]. Instead, they suggested that a single approved version of a RP could act as a "global comparator" during the biosimilar development process, which would reduce costs, and the number of patients needed for clinical studies [141].

Cost of Bridging Studies

Webster and Woollett estimated that the cost of bridging studies ranged from "several hundred thousand to $1 to $2 million US dollars depending on the requirement for clinical studies" [141]. They make the point that these costs will be incurred by every biosimilar applicant in that jurisdiction referencing the same biologic and unable to obtain an adequate quantity of the local RP. They do not mention the time expended by local regulators as they

repetitively examine the results of unnecessary bridging studies involving the same originator product, one approved locally, the other approved and obtained in another jurisdiction.

Commonality of Reference Product Data Across Jurisdictions

Webster and Woollett [141] demonstrate that biosimilar applicants using a foreign-sourced RP may conduct a bridging study between two batches of the same RP. They also point out that "versions of biologics licensed in different jurisdictions usually share the same development data, and any manufacturing changes between versions have been justified by a rigorous comparability process." The authors go on to suggest that because biosimilars are usually licensed in several jurisdictions "in each case as similar to the local reference product," that this "confirms that minor analytical differences between versions of reference biologics are typically inconsequential for clinical outcomes and licensing."

The requirement for a bridging study may seem like a relatively minor unnecessary expense or inconvenience, but the consequences in areas such as the Middle East and North Africa can include creation of "an environment in which neighboring jurisdictions are unable to cooperate effectively and either remain dependent on external suppliers or forgo standards of non-local sourcing" [142].

6.2.2.2 Estimating the Value of Accepting a Global Comparator without a Bridging Study

To estimate the benefit of acceptance of a global comparator without a bridging study, we used a baseline scenario that assumed 40 percent of the study participants were in the United States and 60 percent were in the EU. In this baseline scenario, we assumed a bridging study was required given non-U.S. participants would generally receive the non-U.S. version of the RP. We compared the resulting ENPV to that of a global comparator scenario, in which we assumed that a bridging study was not required, thus lowering the total time and cost of biosimilar drug development. We also assumed that only 20 percent of the study participants would in the United States in the global comparator scenario, i.e., half as many compared to the baseline scenario. The reason for this decrease in U.S. participants is that international studies have less cost and may also be used to support marketing applications in non-U.S. jurisdictions. The baseline assumption that 40 percent of study participants being in the United States is based on FDA data for calendar year (CY) 2019 [143].

6.2.2.3 Results of Global Comparator Incentive Scenario

Table 51, Table 52, and Table 53 present the results of the analyses in which we evaluated the impact of accepting a global comparator without a bridging study as an incentive for biosimilar development. Table 51 presents the results of this analysis given an RP market less than $500 million per year prior to biosimilar entry, Table 52 presents the results given the RP market is greater than $500 million but less than $1 billion per year, and Table 53 presents the results given the RP market is greater than $1 billion per year. Our results show that accepting a global comparator reduces total development costs (-5 percent for markets greater than $1 billion) and expected costs (-5 percent for markets greater than $1 billion), but increases the total expected time for drug development by 0.1 to 0.2 years depending on the size of the market (e.g., 2 percent increase in duration for markets greater than $1 billion). The reductions in total cost are similar (i.e., -5 percent) for biosimilar markets that are greater than

$500 million but less than $1 billion per year and for those that are less than $500 million per year.

Meanwhile, accepting a global comparator without a bridging study increases a biosimilar's ENPV across all market sizes, with the smallest increases in ENPV observed for the largest markets over $1 billion per year. In the scenarios specifically in markets greater than $500 million per year, the first biosimilars to enter the market experience smaller percentage increases in ENPV compared to the fourth or fifth entrants. For example, given a market of $1 billion or greater, the expected ENPV for the first entrant increases by 0.3 percent, the second entrant's ENPV increases by 0.4 percent, the third entrant's ENPV increases by 0.9 percent, and the fourth and fifth entrants' ENPVs increase by 2.9 percent. On the other hand, in scenarios given a market that is less than $500 million per year, the expected ENPV for biosimilars based on entry order is not uniform; the first entrant's ENPV increases by 14.6 percent, the second entrant's ENPV increases by 16.8 percent, the third entrant's ENPV increases by 14.4 percent, and the fourth and fifth entrants' ENPVs increase by 6.5 percent. Importantly, these analyses remove costs of the bridging study, which are roughly fixed. The fixed costs that are removed are a smaller percentage of lifetime revenues in the case of large markets (i.e., over $1 billion) and a larger percentage of lifetime revenues in the case of small markets (i.e., $0–500 million).

Table 51. Estimated Impact on Biosimilars of Accepting a Global Comparator given an RP Market Less Than $500 Million per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	Depends on scenario			
Bridging Study Needed?	Depends on scenario			
CES Needed?	Yes			
Location of CES	Depends on scenario			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline Bridge, 40% US/60% EU	Change Scenario No Bridge, 20% US/80% EU	Difference
Total Cost ($ Million)	All	$130.97 ($85.2, $212.3)	$124.31 ($80.0, $199.4)	-5.1% (-6.1%, -3.9%)
Total Expected Cost ($ Million)		$188.67 ($111.5, $302.7)	$178.61 ($104.2, $283.8)	-5.4% (-6.6%, -4.2%)
Total Capitalized Cost ($ Million)		$205.83 ($122.7, $328.8)	$195.82 ($115.6, $313.3)	-4.8% (-6.5%, -3.2%)
Total Expected Capitalized Cost ($ Million)		$313.78 ($167.0, $480.5)	$298.98 ($157.2, $458.6)	-4.7% (-6.5%, -3.0%)
Total Expected Drug Development Duration (Years)		10.5 (8.6, 12.7)	10.6 (8.9, 12.6)	1.8% (-1.7%, 3.5%)
Total Expected Lifetime Revenues (Million $)	1	$309.49 ($0.7, $1,214.5)		No Change
	2	$204.20		

		($0.5, $801.3)		
	3	$107.64 ($0.3, $422.4)		
	4 or 5	$52.95 ($0.1, $207.8)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$280.26 ($0.7, $1,099.8)		No Change
	2	$183.19 ($0.4, $718.9)		
	3	$96.32 ($0.2, $378.0)		
	4 or 5	$47.26 ($0.1, $185.5)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	-$33.51 (-$424.0, $762.2)	-$18.72 (-$400.1, $772.0)	14.6% (1.4%, 87.8%)
	2	-$130.58 (-$426.8, $412.7)	-$115.79 (-$403.4, $426.5)	16.8% (2.6%, 103.0%)
	3	-$217.45 (-$432.3, $63.6)	-$202.66 (-$408.9, $73.4)	14.4% (3.1%, 58.8%)
	4 or 5	-$266.51 (-$463.6, -$101.3)	-$251.72 (-$441.8, -$91.9)	6.5% (3.0%, 10.6%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 52. Estimated Impact on Biosimilars of Accepting a Global Comparator given an RP Market Greater Than $500 Million but Less Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	Depends on scenario			
Bridging Study Needed?	Depends on scenario			
CES Needed?	Yes			
Location of CES	Depends on scenario			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline Bridge, 40% US/60% EU	Change Scenario No Bridge, 20% US/80% EU	Difference
Total Cost ($ Million)	All	$142.24 ($85.2, $212.3)	$135.01 ($80.0, $199.4)	-5.0% (-6.1%, -3.8%)
Total Expected Cost ($ Million)		$206.70 ($111.5, $302.7)	$195.74 ($104.2, $283.8)	-5.3% (-6.6%, -4.2%)
Total Capitalized Cost ($ Million)		$224.29 ($122.7, $328.8)	$213.67 ($115.6, $313.3)	-4.7% (-6.5%, -3.2%)
Total Expected Capitalized Cost ($ Million)		$344.30 ($167.0, $480.5)	$328.61 ($157.2, $458.6)	-4.5% (-6.5%, -3.0%)
Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)	10.8 (8.9, 12.6)	1.8% (-1.7%, 3.5%)

Total Expected Lifetime Revenues (Million $)	1	$2,001.37 ($1,456.6, $2,622.5)		
	2	$1,320.47 ($961.1, $1,730.3)		
	3	$696.05 ($506.6, $912.1)		No Change
	4 or 5	$342.39 ($249.2, $448.7)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$1,812.36 ($1,319.1, $2,374.8)		
	2	$1,184.65 ($862.2, $1,552.3)		
	3	$622.87 ($453.3, $816.2)		No Change
	4 or 5	$305.63 ($222.4, $400.5)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	$1,468.07 ($868.0, $2,124.3)	$1,483.76 ($890.9, $2,133.8)	1.2% (0.4%, 2.6%)
	2	$840.36 ($411.1, $1,307.2)	$856.05 ($434.1, $1,316.7)	2.3% (0.7%, 5.6%)
	3	$278.58 ($2.3, $574.4)	$294.27 ($25.2, $583.8)	15.3% (1.6%, 79.3%)
	4 or 5	-$38.66 (-$228.6, $188.3)	-$22.98 (-$205.7, $198.1)	55.3% (5.2%, 386.0%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 53. Estimated Impact on Biosimilars of Accepting a Global Comparator given an RP Market Greater Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	Depends on scenario			
Bridging Study Needed?	Depends on scenario			
CES Needed?	Yes			
Location of CES	Depends on scenario			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline Bridge, 40% US/60% EU	Change Scenario No Bridge, 20% US/80% EU	Difference
Total Cost ($ Million)	All	$135.35 ($90.1, $206.2)	$129.19 ($85.1, $194.8)	-4.5% (-5.6%, -3.9%)
Total Expected Cost ($ Million)		$199.24 ($118.3, $304.6)	$189.64 ($111.1, $287.5)	-4.8% (-6.0%, -4.2%)
Total Capitalized Cost ($ Million)		$212.18 ($130.5, $329.1)	$203.14 ($123.8, $313.7)	-4.1% (-5.8%, -3.2%)

Total Expected Capitalized Cost ($ Million)		$331.59 ($177.6, $508.0)	$318.11 ($168.4, $485.5)	-3.9% (-5.6%, -3.0%)
Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)	10.8 (8.9, 12.6)	2.0% (-0.8%, 3.5%)
Total Expected Lifetime Revenues (Million $)	1	$10,847.78 ($3,127.5, $44,624.4)		
	2	$7,157.17 ($2,063.5, $29,442.4)		
	3	$3,772.73 ($1,087.7, $15,519.9)		No Change
	4 or 5	$1,855.82 ($535.1, $7,634.3)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$9,823.32 ($2,832.1, $40,410.1)		
	2	$6,421.03 ($1,851.2, $26,414.1)		
	3	$3,376.09 ($973.4, $13,888.2)		No Change
	4 or 5	$1,656.58 ($477.6, $6,814.7)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	$9,491.73 ($2,543.7, $40,002.8)	$9,505.21 ($2,553.5, $40,024.5)	0.3% (0.0%, 0.7%)
	2	$6,089.43 ($1,562.8, $26,006.8)	$6,102.92 ($1,572.6, $26,028.5)	0.4% (0.1%, 1.2%)
	3	$3,044.50 ($699.2, $13,480.9)	$3,057.98 ($709.1, $13,502.6)	0.9% (0.1%, 2.7%)
	4 or 5	$1,324.99 ($202.9, $6,407.4)	$1,338.48 ($216.5, $6,429.1)	2.9% (0.2%, 11.1%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

6.2.3 Eliminating the Requirement for CESs

Although switching studies and bridging studies have attracted some robust skepticism regarding their utility in ensuring the safety and effectiveness of proposed biosimilars [144], the major focus of experts and stakeholders seeking to streamline biosimilar approval has been the CES that has been a *sine qua non* for all but a few biosimilar BLAs to date [145] [123] [146] [24, 25].

As large and expensive phase 3 trials have not shown their ability to detect clinical differences between biosimilars and originators, it is fathomable that in the coming years, a stronger chemistry, manufacturing, and controls (CMC)/phase I package together with meaningful post-approval studies could replace the current development paradigm that is based on large, phase 3 studies [144].

6.2.3.1 Replacing the CES as an Incentive for Biosimilar Development

The immediate value of avoiding a CES is substantial—they are expensive and time consuming.[50] Critics of the CESs offer several compelling points: (1) CESs are unnecessary to confirm clinical efficacy. By the time the biosimilar reaches this stage of development, it has been subject to extensive and exacting in vitro analysis, as well as PK/PD similarity comparative PK/PD testing. Given its structural similarity to the RP and its closely matching test results, its comparable clinical efficacy is virtually a forgone conclusion. (2) The clinical endpoints of the comparative efficacy study often lack sensitivity to discriminate at the level of the small differences as observed between biosimilars and RPs, whereas in-vitro structural and functional analyses have a greater capacity to detect them. (3) Comparative efficacy study results are extremely unlikely to reveal an issue of efficacy or safety that results in non-approval of the biosimilar. One investigator examined 90 biosimilar marketing applications submitted to EMA. He reported: "Of these, the search revealed that only seven were rejected by CHMP or withdrawn by the applicant prior to probable rejection. ... In every case, quality and manufacturing concerns were cited as the major reasons for lack (or potential lack) of approval.... This suggests that it is the quality data, rather than the clinical data, that is acting as the gate-keeper to biosimilar approval" [147].[51] Another author has agreed but pointed out that the reverse was not true: "Clinical efficacy testing used to overcome differences in the analytical, nonclinical, and clinical pharmacology comparisons can lead to the approval of unsafe products" [148].

Dr. Niazi also observed that, "The main issue is the mindset of the stakeholders, particularly the prescribers, who are used to seeing such studies to gain confidence in a new product" [148]. This observation has been supported by surveys of prescribers and dispensers regarding their attitudes toward biosimilars, and what kind of evidence might make them (or their reluctant colleagues) more likely to prescribe a biosimilar. In addition, in our interviews with biosimilar industry representatives, some voiced the opinion that if CESs might be waived, it would be important to know as early as possible, as much of the planning and some of the expenses of conducting comparative efficacy studies happen early in development. Although regulators have shown increasing flexibility about the need for CESs, making this determination on a "case-by-case" basis may offer little help to biosimilar sponsors unless that determination comes very early in development. (One of our interviewees said, "Until we know for sure we won't need it [a comparative efficacy study], we have to assume we will.") The need for an early determination from FDA as to whether a comparative efficacy study should be performed, plus the apparent marketing value of a successful comparative efficacy study, apparently have combined to make comparative efficacy studies a persistent part of the development and approval of many biosimilars.

[50] Estimates of phase III costs and duration have had a wide range. A study by Moore et al. [155] of 29 phase III trials performed in support of all 23 biosimilars approved at the time of the study reported median enrollment of 504 patient/subjects; a median cost of $20.8 million (IQR $13.8 mil.–$35.3 mil.); and median treatment duration of 52 weeks [155]. The authors also reported that the biosimilar phase III trials "appeared to be as rigorous as and often larger, longer, and more costly than pivotal trials for new molecular entities" [155].

[51] The same author added, "It is also interesting to note that quality data have been successfully used to support approval in cases where the clinical primary efficacy endpoint was not met" [146].

6.2.3.2 Replacing the Comparative Efficacy Study Clinical Efficacy Study

To model the benefit of removing the comparative efficacy study, we used a baseline scenario that included time and cost. In this baseline scenario, we assumed that 40 percent of study participants were in the United States (with the other 60 percent being in the EU), that a mix of healthy and sick participants were needed for the PK/PD similarity study, and that a switching study was not performed. We compared this scenario to a no-CES scenario that was identical except for (a) the removal of the CES and (b) a longer and more costly PK/PD similarity study. Seven biosimilar drugs have been approved without any clinical efficacy data: filgrastim-aafi, filgrastim-sndz, filgrastim-ayow, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-pbbk, and epoetin alfa-epbx [148]. In these cases, FDA has required PK and PD PK/PD similarity study biomarker data, which can extend the length and cost of the PK/PD similarity study. To determine the increase in cost and length, we compared the PK/PD similarity study data for these seven biosimilars (all of which are used in oncology) to the cost and length of PK/PD similarity studies for other oncology biosimilars that did perform a CES. We found that if a CES was not performed, the PK/PD similarity study was 79.7 percent longer and 36.8 percent more expensive than if a CES were performed (owing to a greater number of study subjects). We therefore increased the PK/PD similarity duration and cost by these factors in the no-CES scenario.

6.2.3.3 Results of Comparative Efficacy Study (CES) Replacement Incentive Scenario

Table 54, Table 55, and Table 56 present the results of the analyses in which we evaluated the impact of replacing the CES with longer and more costly PK/PD similarity studies as an incentive for biosimilar development. Table 54 presents the results of this analysis given an RP market less than $500 million per year prior to biosimilar entry, Table 55 presents the results given the RP market is greater than $500 million but less than $1 billion per year, and Table 56 presents the results given the RP market is greater than $1 billion per year. Our results show that replacing the CES with larger PK/PD similarity studies reduces total development costs (-18 percent for markets greater than $1 billion) and expected costs (-21 percent for markets greater than $1 billion) as well as the total expected time for drug development (-8 percent for markets greater than $1 billion). The reductions in cost and time are similar for biosimilar markets that are greater than $500 million but less than $1 billion per year and for those that are less than $500 million per year.

Meanwhile, removing the CES in favor of larger PK/PD similarity studies increases a biosimilar's ENPV across all market sizes, with the smallest increases in ENPV observed for the largest markets over $1 billion per year. In the scenarios specifically in which we replace the CES with larger PK/PD similarity studies given a market greater than $500 million per year, the first biosimilars to enter the market experience smaller increases in ENPV compared to the fourth or fifth entrants. For example, given a market of $1 billion or greater, the expected ENPV for the first entrant increases by 1.6 percent, the second entrant's ENPV increases by 2.5 percent, the third entrant's ENPV increases by 5.4 percent, and the fourth and fifth entrants' ENPVs increase by 17.0 percent. On the other hand, in the scenario in which we replace the CES with a larger PK/PD similarity study given a market that is less than $500 million per year, the expected ENPV for biosimilars based on entry order is not uniform; the first entrant ENPV increases by 80.6

percent, the second entrant ENPV increases by 94.3 percent, the third entrant ENPV increases by 87.0%, and the fourth and fifth entrants' ENPVs increase by 38.1 percent. Importantly, these analyses remove the costs of the CES, which are roughly fixed. The fixed costs that are removed are a smaller percentage of lifetime revenues in the case of large markets (i.e., over $1 billion) and a larger percentage of lifetime revenues in the case of small markets (i.e., $0–500 million).

Table 54. Estimated Impact on Biosimilars of Replacing Clinical Efficacy Studies given an RP Market Less Than $500 Million per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Depends on scenario			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable	Biosimilar Entry Order	Baseline CES	Change Scenario Larger PK/PD similarity Study, No CES	Difference
Total Cost ($ Million)	All	$130.97 ($85.2, $212.3)	$106.37 ($65.8, $181.9)	-19.1% (-24.6%, -14.3%)
Total Expected Cost ($ Million)		$188.67 ($111.5, $302.7)	$147.58 ($82.5, $244.7)	-22.2% (-27.8%, -18.1%)
Total Capitalized Cost ($ Million)		$205.83 ($122.7, $328.8)	$158.22 ($88.8, $263.2)	-23.5% (-29.5%, -19.9%)
Total Expected Capitalized Cost ($ Million)		$313.78 ($167.0, $480.5)	$230.50 ($115.0, $360.6)	-26.9% (-32.8%, -23.2%)
Total Expected Drug Development Duration (Years)		10.5 (8.6, 12.7)	9.6 (7.7, 11.9)	-8.5% (-10.5%, -6.3%)
Total Expected Lifetime Revenues (Million $)	1	$309.49 ($0.7, $1,214.5)		No Change
	2	$204.20 ($0.5, $801.3)		
	3	$107.64 ($0.3, $422.4)		
	4 or 5	$52.95 ($0.1, $207.8)		
	1	$280.26		

Total Expected Lifetime Revenues, Discounted (Million $)			($0.7, $1,099.8)	No Change
	2		$183.19 ($0.4, $718.9)	
	3		$96.32 ($0.2, $378.0)	
	4 or 5		$47.26 ($0.1, $185.5)	
ENPV over Biosimilar Product's Lifetime (Million $)	1	-$33.51 (-$424.0, $762.2)	$49.77 (-$308.7, $850.3)	80.6% (9.4%, 556.6%)
	2	-$130.58 (-$426.8, $412.7)	-$47.30 (-$310.6, $483.2)	94.3% (18.3%, 576.5%)
	3	-$217.45 (-$432.3, $63.6)	-$134.17 (-$316.2, $140.2)	87.0% (23.4%, 372.2%)
	4 or 5	-$266.51 (-$463.6, -$101.3)	-$183.23 (-$336.1, -$32.4)	38.1% (23.3%, 67.8%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 55. Estimated Impact on Biosimilars of Replacing Clinical Efficacy Studies given an RP Market Greater Than $500 Million but Less Than $1 Billion per Year Prior to Biosimilar Entry

Parameters	
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)
Location of PK/PD similarity Study	40% US and 60% EU
Bridging Study Needed?	Yes
CES Needed?	Depends on scenario
Location of CES	40% US and 60% EU
Switching Study Needed?	No
Device Development Needed?	No
PAI Needed?	Yes
Number of Years in Market	10 years
Opportunity Cost of Capital	8.20%

Results				
Outcome Variable	Biosimilar Entry Order	Baseline	Change Scenario	Difference
		CES	Larger PK/PD similarity Study, No CES	
Total Cost ($ Million)	All	$142.24 ($85.2, $212.3)	$116.84 ($65.8, $181.9)	-18.2% (-23.0%, -14.3%)
Total Expected Cost ($ Million)		$206.70 ($111.5, $302.7)	$163.20 ($82.5, $244.7)	-21.4% (-26.1%, -18.2%)
Total Capitalized Cost ($ Million)		$224.29 ($122.7, $328.8)	$174.19 ($88.8, $263.2)	-22.7% (-27.7%, -20.0%)
Total Expected Capitalized Cost ($ Million)		$344.30 ($167.0, $480.5)	$254.99 ($115.0, $360.6)	-26.2% (-31.2%, -23.2%)

Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)	9.7 (7.7, 11.9)	-8.4% (-10.5%, -6.3%)
Total Expected Lifetime Revenues (Million $)	1	$2,001.37 ($1,456.6, $2,622.5)		
	2	$1,320.47 ($961.1, $1,730.3)		
	3	$696.05 ($506.6, $912.1)		No Change
	4 or 5	$342.39 ($249.2, $448.7)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$1,812.36 ($1,319.1, $2,374.8)		
	2	$1,184.65 ($862.2, $1,552.3)		
	3	$622.87 ($453.3, $816.2)		No Change
	4 or 5	$305.63 ($222.4, $400.5)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	$1,468.07 ($868.0, $2,124.3)	$1,557.38 ($985.3, $2,187.6)	6.8% (2.7%, 13.5%)
	2	$840.36 ($411.1, $1,307.2)	$929.67 ($528.4, $1,370.5)	12.6% (4.3%, 28.7%)
	3	$278.58 ($2.3, $574.4)	$367.89 ($119.6, $638.9)	80.4% (9.4%, 406.6%)
	4 or 5	-$38.66 (-$228.6, $188.3)	$50.65 (-$111.3, $240.3)	415.2% (27.8%, 3142.2%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

Table 56. Estimated Impact on Biosimilars of Replacing Clinical Efficacy Studies given an RP Market Greater Than $1 Billion per Year Prior to Biosimilar Entry

Parameters				
Type of PK/PD similarity Study Needed	Mixed (Healthy Subjects and Patients)			
Location of PK/PD similarity Study	40% US and 60% EU			
Bridging Study Needed?	Yes			
CES Needed?	Depends on scenario			
Location of CES	40% US and 60% EU			
Switching Study Needed?	No			
Device Development Needed?	No			
PAI Needed?	Yes			
Number of Years in Market	10 years			
Opportunity Cost of Capital	8.20%			
Results				
Outcome Variable		Baseline	Change Scenario	Difference

	Biosimilar Entry Order	CES	Larger PK/PD similarity Study, No CES	
Total Cost ($ Million)	All	$135.35 ($90.1, $206.2)	$111.34 ($68.0, $175.3)	-17.8% (-24.6%, -13.9%)
Total Expected Cost ($ Million)		$199.24 ($118.3, $304.6)	$158.32 ($85.4, $246.3)	-20.6% (-27.8%, -17.9%)
Total Capitalized Cost ($ Million)		$212.18 ($130.5, $329.1)	$165.35 ($92.0, $263.1)	-22.2% (-29.5%, -19.1%)
Total Expected Capitalized Cost ($ Million)		$331.59 ($177.6, $508.0)	$247.54 ($119.3, $383.3)	-25.4% (-32.8%, -23.2%)
Total Expected Drug Development Duration (Years)		10.6 (8.6, 12.7)	9.8 (7.7, 11.9)	-8.4% (-10.5%, -6.3%)
Total Expected Lifetime Revenues (Million $)	1	$10,847.78 ($3,127.5, $44,624.4)		No Change
	2	$7,157.17 ($2,063.5, $29,442.4)		
	3	$3,772.73 ($1,087.7, $15,519.9)		
	4 or 5	$1,855.82 ($535.1, $7,634.3)		
Total Expected Lifetime Revenues, Discounted (Million $)	1	$9,823.32 ($2,832.1, $40,410.1)		No Change
	2	$6,421.03 ($1,851.2, $26,414.1)		
	3	$3,376.09 ($973.4, $13,888.2)		
	4 or 5	$1,656.58 ($477.6, $6,814.7)		
ENPV over Biosimilar Product's Lifetime (Million $)	1	$9,491.73 ($2,543.7, $40,002.8)	$9,575.79 ($2,611.8, $40,111.9)	1.6% (0.3%, 3.4%)
	2	$6,089.43 ($1,562.8, $26,006.8)	$6,173.49 ($1,630.8, $26,115.9)	2.5% (0.4%, 5.6%)
	3	$3,044.50 ($699.2, $13,480.9)	$3,128.55 ($760.2, $13,590.0)	5.4% (0.8%, 13.1%)
	4 or 5	$1,324.99 ($202.9, $6,407.4)	$1,409.05 ($276.3, $6,516.4)	17.0% (1.7%, 53.5%)

CES = clinical efficacy and safety; PAI = pre-approval inspection; ENPV = expected net present value
Note: Values in parentheses show the 95% CI across all products.

7 DISCUSSION AND CONCLUSION

It is important for regulators and policy makers to optimize their understanding of biosimilar/biologic market dynamics to craft policies that promote price competition and broaden access to these therapies. Our purpose was to develop a functional model of the costs and revenues that could be expected to result from development, approval, and entry of a given biosimilar into markets of varied attributes, competitive conditions, regulatory requirements, and legal challenges. The model developed is based on extensive research into historical and current market dynamics, detailed analysis of biologic and biosimilar sales data,

and semi-structured interviews with twenty SMEs from industry, academia, and government involved in biosimilar/biologic development, commercialization, and utilization.

The major variables we considered in constructing the model were: the type and location of the PK/PD similarity studies; the need for a bridging study, a comparative efficacy study, and/or a switching study; patent litigation, device development if required; an FDA pre-approval inspection; the number of years in the market, and the opportunity cost of capital. Market size (measured by dollar sales of the RP in the year before first biosimilar entry) and market entry order had substantial impacts on expected earnings.

Average Biosimilar Development Costs. The total cost of development and approval for an average biosimilar is about $135 million for RP markets with sales greater than $1 billion annually without biosimilar competition, about $142 million for RP markets between $500 million and $1 billion, and about $131 million for markets less than $500 million. When we account for the cost of failed development programs, the average expected cost per approved biosimilar product is approximately $60 million higher for all RP market sizes. From initiating development to biosimilar launch, cost factors fell into six categories, or stages. We calculated the share of costs for each stage for each of the three RP market sizes, There was little variation in cost share percentages across market sizes. Cost shares in large markets (>$1 billion markets) were: 10 percent for pre-clinical stage, 27 percent for phase 1 stage, 42 percent for CES stage, 1% for FDA application and approval stage, 12 percent for IP litigation, and 8 percent for commercialization.

Average Biosimilar Lifetime Revenues and ENPV. For an average biosimilar, we found that market size and entry order were determinative of revenues over the market life of the biosimilar. In large markets, lifetime ENPV ranged from $9.5 billion for the first biosimilar entrant to $1.3 billion for the fourth and fifth entrants. In medium markets, the first biosimilar's lifetime ENPV is $1.5 billion, but falls to –$38.7 million for the fourth and fifth market entrants. For markets smaller than $500 million, lifetime ENPV is decidedly negative for all entrants, ranging from –$33.5 million for the first entrant to –$266.5 million for the fourth and fifth entrants. (This outcome supports the observation of several SMEs interviewed for the study that $500 million is about the smallest RP market that a biosimilar company might consider entering.)

Costs of Select Barriers to Entry and the Value of Incentives Designed to Mitigate or Eliminate Select Barries on ENPV. Using the functional model developed for the study, we examined the impact of three barriers on cost of development and the effect of incentives designed to mitigate or eliminate those barriers on the ENPV for a biosimilar developer. The estimates for these impacts varied by biosimilar market attributes, e.g., number of market entrants, size of market. We highlight our key findings for large markets (greater than equal to annual revenues of $1 billion) for each below.

- *Automatic interchangeability – Designating all approved biosimilars to be interchangeable with the RP. Large market cost savings = None; Large market increase in lifetime ENPV = $2 billion (20.6 percent).* BPCIA established an interchangeable designation for biosimilars that could be earned by submitting suitable data from additional clinical switching studies. Interchangeable designation, as described in BPCIA, would enable pharmacists to substitute the interchangeable

for a prescribed RP. This established what was often viewed as a higher order of biosimilars and may have undercut biosimilar uptake in the United States. Generic drugs, in contrast, are interchangeable with their reference brand drugs without further testing. We therefore used generic drug uptake data as a basis to approximate the "faster uptake" that would accrue to biosimilars with universal interchangeable designation. Although development costs remained unchanged, an improved uptake rate of biosimilars generated an increase in lifetime ENPV of $2 billion, or 20.6 percent.

- *Establishing a Global Comparator. Large market cost savings = $5.1 million (4.5 percent); Large market increase in lifetime ENPV = $13.5 million.* The use of a global comparator facilitates biosimilar development by eliminating the need to perform a bridging study to establish identity of the FDA-approved RP and a foreign-sourced RP.
- *Eliminating the requirement for comparative efficacy studies. Large market cost savings = $24 million (17.8 percent); Large market increase in lifetime ENPV = $84 million.* Although CESs are the highest cost element of preparing a biosimilar for market entry, our assumption is that, in the absence of CESs, more robust in vitro and PK/PD similarity studies will be needed to offset any residual uncertainties related to the biosimilar. Hence the savings provided by this incentive will fall short of the previously established costs of CES.

Taken together, these three incentives could save the average large market biosimilar candidate $29.1 million in development costs and provide an additional $2+ billion in lifetime ENPV.

In our analysis, the lowering of the barrier to interchangeability by eliminating the switching study as a requirement does not powerfully affect lifetime ENPV. This is because, while the cost component of the barrier is gone, the two tiers of biosimilar remain to cloud the rate of uptake. In contrast, designating interchangeability as a property of all approved biosimilars is expected to increase uptake for all biosimilars.

Our study had several limitations. First, our sample size was small, and the amount of time in market too short, to account for several other factors that affect sales and market uptake, including, e.g., type of pathology treated (i.e., acute vs chronic), spacing of entrants' launch dates, medical benefit vs pharmacy benefit, etc.). Second, our estimates of net sales may not have accounted for all rebates and discounts, which may have resulted in overestimation of sales for the biosimilars as well as their RPs. Third, regulatory policies have been shifting over the period of the study, as FDA moves away from requiring CES, and encourages applicants to pursue interchangeability designation, and CMS's reimbursement practices that effectively make all biosimilars interchangeable. Finally, most of the parameter estimates used in the model were expert opinion based and thus subject to recall, motivational, and other biases.

Given the constantly evolving landscape, further research on development costs and market entry decisions is warranted. A closer examination of formulary coverage for biosimilars could also help inform policy discussions regarding PBM practices. For example, relatively

recently, two of the largest PBMs removed the best-selling original biologics from their formularies in favor of biosimilars, an apparent reversal from their past practice of excluding or up-tiering biosimilars in favor of RPs. Another interesting strand of research could investigate differences in frequency and severity of adverse events reported to FDA from biosimilars vs their RPs, and biosimilars vs biosimilars with waived CES. Results of such a study may help inform provider prescription practices.

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APPENDIX A: BIOSIMILARS APPROVED IN EU, CANADA, JAPAN, AUSTRALIA

Table 57. Europe: EMA Approved Biosimilars in Market as of May 23, 2024

No.	Product Name	Active Substance	Authorization Date	Manufacturer/Company Name
1	Amgevita	adalimumab	21-Mar-17	Amgen
2	Amsparity	adalimumab	13-Feb-20	Pfizer
3	Hefiya	adalimumab	26-Jul-18	Sandoz
4	Hukyndra	adalimumab	15-Nov-21	Alvotech/Stada Artnimettel
5	Hulio	adalimumab	17-Sep-18	Mylan/Fujifilm Kyowa Kirin Biologics
6	Hyrimoz	adalimumab	26-Jul-18	Sandoz
7	Idacio	adalimumab	2-Apr-19	Fresenius Kabi
8	Imraldi	adalimumab	24-Aug-17	Samsung Bioepis
9	Libmyris	adalimumab	12-Nov-21	Alvotech/Stada Artnimettel
10	Yuflyma	adalimumab	11-Feb-21	Celltrion Healthcare
11	Yesafili	aflibercept	15-Sep-23	Biocon/Viatris (formerly Mylan)
12	Abevmy	bevacizumab	21-Apr-21	Mylan (now Viatris)
13	Alymsys	bevacizumab	26-Mar-21	mAbxience Research
14	Aybintio	bevacizumab	19-Aug-20	Samsung Bioepis
15	Avzivi	bevacizumab	CHMP positive opinion 30-May-24	Bio-Thera Solutions
16	Mvasi	bevacizumab	15-Jan-18	Amgen
17	Onbevzi	bevacizumab	11-Jan-21	Samsung Bioepis
18	Oyavas	bevacizumab	26-Mar-21	Stada Arzneimittel
19	Vegzelma	bevacizumab	17-Aug-22	Celltrion Healthcare
20	Zirabev	bevacizumab	14-Feb-19	Pfizer
21	Jubbonti	denosumab	16-May-24	Sandoz GmbH
22	Wyost	denosumab	16 May 2024	Sandoz GmbH
23	Bekemv	eculizumab	24-Feb-23	Amgen
24	Epysqli	eculizumab	26-May-23; 22-Mar-24 (for aHUS)	Samsung Bioepis
25	Enoxaparin BECAT	enoxaparin sodium	24-Mar-17	Laboratorios ROVI
26	Inhixa	enoxaparin sodium	15-Sep-16	Techdow Europe
27	Abseamed	epoetin alfa	27-Aug-07	Medice Arzneimittel Pütter
28	Binocrit	epoetin alfa	28-Aug-07	Sandoz
29	Epoetin alfa Hexal	epoetin alfa	27-Aug-07	Hexal
30	Retacrit	epoetin zeta	18-Dec-07	Hospira (Pfizer)
31	Silapo	epoetin zeta	18-Dec-07	Stada Arzneimittel
32	Benepali	etanercept	13-Jan-16	Samsung Bioepis
33	Erelzi	etanercept	23-Jun-17	Sandoz
34	Nepexto	etanercept	25-May-20	Mylan
35	Accofil	filgrastim	17-Sep-14	Accord Healthcare
36	Filgrastim Hexal	filgrastim	6-Feb-09	Hexal
37	Grastofil	filgrastim	17-Oct-13	Apotex
38	Nivestim	filgrastim	7-Jun-10	Hospira (Pfizer)
39	Ratiograstim	filgrastim	15-Sep-08	Ratiopharm
40	Tevagrastim	filgrastim	15-Sep-08	Teva Generics
41	Zarzio	filgrastim	6-Feb-09	Sandoz

No.	Product Name	Active Substance	Authorization Date	Manufacturer/Company Name
42	Bemfola	follitropin alfa	26-Mar-14	Finox Biotech
43	Ovaleap	follitropin alfa	27-Sep-13	Teva Pharma
44	Flixabi	infliximab	26-May-16	Samsung Bioepis
45	Inflectra	infliximab	10-Sep-13	Hospira (Pfizer)
46	Remsima	infliximab	10-Sep-13	Celltrion
47	Zessly	infliximab	18-May-18	Sandoz
48	Insulin aspart Sanofi	insulin aspart	25-Jun-20	Sanofi-Aventis
49	Kirsty (previously Kixelle)	insulin aspart	5-Feb-21	Biocon/Viatris (formerly Mylan)
50	Truvelog Mix 30	insulin aspart	Apr-22	Sanofi-Aventis
51	Abasaglar (previously Abasria)	insulin glargine	9-Sep-14	Eli Lilly/Boehringer Ingelheim
52	Semglee	insulin glargine	28-Mar-18	Biocon/Viatris (formerly Mylan)
53	Insulin lispro Sanofi	insulin lispro	18 Jul 2017	Sanofi-Aventis
54	Tyruko	natalizumab	26-Sep-23	Sandoz GmbH
55	Omlyclo	omalizumab	23-May-24	Celltrion Healthcare
56	Cegfila (previously Pegfilgrastim Mundipharma)	pegfilgrastim	19-Dec-19	Mundipharma Biologics
57	Fulphila	pegfilgrastim	20-Nov-18	Mylan
58	Grasustek	pegfilgrastim	20-Jun-19	Juta Pharma (USV)
59	Nyvepria	pegfilgrastim	18-Nov-20	Pfizer
60	Pelgraz	pegfilgrastim	21-Sep-18	Accord Healthcare
61	Pelmeg	pegfilgrastim	20-Nov-18	Cinfa Biotech/ Mundipharma
62	Stimufend	pegfilgrastim	24-Mar-22	Fresenius Kabi
63	Ziextenzo	pegfilgrastim	22-Nov-18	Sandoz
64	Byooviz	ranibizumab	18-Aug-21	Samsung Bioepis
65	Ranivisio	ranibizumab	25-Aug-22	Bioeq/Teva Pharma
66	Rimmyrah	ranibizumab	5-Jan-24	Qilu Pharma
67	Ximluci	ranibizumab	9-Nov-22	Stada Arzneimittel/Xbrane Biopharma
68	Blitzima	rituximab	13-Jul-17	Celltrion
69	Rixathon	rituximab	15-Jun-17	Sandoz
70	Riximyo	rituximab	15-Jun-17	Sandoz
71	Ruxience	rituximab	1-Apr-20	Pfizer
72	Truxima	rituximab	17-Feb-17	Celltrion Healthcare
73	Omnitrope	somatropin	12-Apr-06	Sandoz
74	Livogiva	teriparatide	27-Aug-20	Theramex Ireland
75	Movymia	teriparatide	11-Jan-17	Stada Arzneimittel
76	Sondelbay	teriparatide	24-Mar-22	Accord Healthcare
77	Terrosa	teriparatide	4-Jan-17	Gedeon Richter
78	Tofidence	tocilizumab	CHMP positive opinion 25-Apr-24	Biogen
79	Tyenne	tocilizumab	15-Sep-23	Fresenius Kabi Deutschland GmbH
80	Herzuma	trastuzumab	8-Feb-18	Celltrion Healthcare
81	Herwenda	trastuzumab	15-Nov-23	Sandoz GmbH
82	Kanjinti	trastuzumab	16-May-18	Amgen/Allergan
83	Ogivri	trastuzumab	12-Dec-18	Biocon/Mylan
84	Ontruzant	trastuzumab	15 Nov 2017	Samsung Bioepis

No.	Product Name	Active Substance	Authorization Date	Manufacturer/Company Name
85	Trazimera	trastuzumab	26-Jul-18	Pfizer
86	Zercepac	trastuzumab	27-Jul-20	Accord Healthcare
87	Pyzchiva	ustekinumab	22-Apr-24	Samsung Bioepis
88	Uzpruvo	ustekinumab	5-Jan-24	Alvotech/Stada Arzneimittel AG
89	Wezenla	ustekinumab	CHMP positive opinion 25-Apr-24	Amgen

Source: EMA
Data updated as of May 23, 2024. 17 additional approved biosimilars have been withdrawn after approval.
CHMP = Committee for Medicinal Products for Human Use; IVF = in vitro fertilization.

Table 58. Canada: Biosimilars Approved by Health Canada, as of March 21, 2024

No.	Approval Time	Biosimilar Name N=56	Proper Name N=17	Biosimilar Company (Approval Date)	Reference Product (Company)
1	748 days	OMNITROPE	somatropin	Sandoz (April 2009)	GENOTROPIN (Pfizer)
2	427 days	INFLECTRA	Infliximab	Hospira (January 2014)	REMICADE (Janssen)
3	427 days	REMSIMA (subcutaneous version marketed as REMSIMA SC)	Infliximab	Celltrion (January 2014)	REMICADE (Janssen)
4	356 days	BASAGLAR	insulin glargine	Eli Lilly (August 2015)	LANTUS (Sanofi-Aventis)
5	1039 days	GRASTOFIL [a]	Filgrastim	Apotex (December 2015)	NEUPOGEN (Amgen)
6	358 days	BRENZYS	etanercept	Samsung Bioepis (May 2016)	ENBREL (Immunex)
7	353 days	ERELZI	etanercept	Sandoz (April 2017)	ENBREL (Immunex)
8	351 days	ADMELOG, ADMELOG HP	insulin lispro	Sanofi-aventis (November 2017)	HUMALOG (Eli Lilly)
9	793 days	RENFLEXIS	Infliximab	Samsung Bioepis (December 2017)	REMICADE (Janssen)
10	432 days	HADLIMA, HADLIMA PUSHTOUCH	adalimumab	Samsung Bioepis (May 2018)	HUMIRA (AbbVie)
11	349 days	LAPELGA	pegfilgrastim	Apotex (April 2018)	NEULASTA (Amgen)
12	358 days	MVASI	bevacizumab	Amgen (December 2017)	AVASTIN (Hoffmann La Roche)
13	754 days	FULPHILA	pegfilgrastim	Mylan (December 2018)	NEULASTA (Amgen)
14	335 days	TRUXIMA	Rituximab	Celltrion (July 2018)	RITUXAN (Hoffmann La Roche)
15	356 days	OGIVRI	trastuzumab	BGP Pharma (March 2018)	HERCEPTIN (Hoffmann La Roche)
16	336 days	ZIRABEV	bevacizumab	Pfizer (June 2019)	AVASTIN (Hoffmann La Roche)
17	348 days	TRAZIMERA	trastuzumab	Pfizer (November 2018)	HERCEPTIN (Hoffmann La Roche)
18	324 days	HERZUMA	trastuzumab	Celltrion (September 2018)	HERCEPTIN (Hoffmann La Roche)
19	637 days	OSNUVO	teriparatide	Avir Pharma (January 2020)	FORTEO (Eli Lilly)
20	920 days	KANJINTI	trastuzumab	Amgen (February 2020)	HERCEPTIN (Hoffmann La Roche)
21	351 days	AVSOLA	Infliximab	Amgen (March 2020)	REMICADE (Janssen)
22	345 days	NIVESTYM	Filgrastim	Pfizer (April 2020)	NEUPOGEN (Amgen)

No.	Approval Time	Biosimilar Name N=56	Proper Name N=17	Biosimilar Company (Approval Date)	Reference Product (Company)
23	336 days	ZIEXTENZO	pegfilgrastim	Sandoz (April 2020)	NEULASTA (Amgen)
24	795 days	RIXIMYO	Rituximab	Sandoz (April 2020)	RITUXAN (Hoffmann La Roche)
25	344 days	RUXIENCE	Rituximab	Pfizer (May 2020)	RITUXAN (Hoffmann La Roche)
26	349 days	NOROMBY, NOROMBY HP	enoxaparin sodium	Juno (October 2020)	LOVENOX, LOVENOX HP (Sanofi)
27	351 days	TRURAPI	insulin aspart	Sanofi (October 2020)	NOVORAPID (Novo Nordisk)
28	352 days	NYVEPRIA	pegfilgrastim	Pfizer (October 2020)	NEULASTA (Amgen)
29	346 days	IDACIO	adalimumab	Fresenius Kabi (October 2020)	HUMIRA (Abbvie)
30	350 days	AMGEVITA	adalimumab	Amgen (November 2020)	HUMIRA (Abbvie)
31	348 days	HYRIMOZ	adalimumab	Sandoz (November 2020)	HUMIRA (Abbvie)
32	345 days	INCLUNOX, INCLUNOX HP	enoxaparin sodium	Sandoz (November 2020)	LOVENOX, LOVENOX HP (Sanofi)
33	348 days	HULIO	adalimumab	BGP Pharma (November 2020)	HUMIRA (Abbvie)
34	444 days	REDESCA, REDESCA HP	enoxaparin sodium	Shenzhen Techdow (December 2020)	LOVENOX, LOVENOX HP (Sanofi)
35	349 days	ABRILADA	adalimumab	Pfizer (January 2021)	HUMIRA (Abbvie)
36	346 days	RIABNI	Rituximab	Amgen (March 2021)	RITUXAN (Hoffmann La Roche)
37	363 days	BAMBEVI	bevacizumab	Apotex (September 2021)	AVASTIN (Hoffmann La Roche)
38	997 days	NYPOZI	Filgrastim	Tanvex Biopharma (October 2021)	NEUPOGEN (Amgen)
39	347 days	KIRSTY	insulin aspart	BGP Pharma (October 2021)	NOVORAPID (Novo Nordisk)
40	526 days	ABEVMY	bevacizumab	BGP Pharma (November 2021)	AVASTIN (Hoffmann La Roche)
41	354 days	AYBINTIO	bevacizumab	Samsung Bioepis (November 2021)	AVASTIN (Hoffmann La Roche)
42	347 days	IXIFI	Infliximab	Pfizer (December 2021)	REMICADE (Janssen)
43	359 days	YUFLYMA	adalimumab	Celltrion (December 2021)	HUMIRA (AbbVie)
44	379 days	SIMLANDI	adalimumab	JAMP Pharma (January 2022)	HUMIRA (AbbVie)
45	718 days	ONTRUZANT	trastuzumab	Samsung Bioepis (January 2022)	HERCEPTIN (Hoffmann La Roche)
46	344 days	BYOOVIZ	ranibizumab	Samsung Bioepis (March 2022)	LUCENTIS (Novartis)
47	350 days	SEMGLEE	insulin glargine	BGP Pharma (April 2022)	LANTUS (Sanofi-Aventis)
48	477 days	MYXREDLIN	human insulin (recombinant)	Baxter (August 2022)	NOVOLIN GE (Novo Nordisk)
49	986 days	RYMTI	etanercept	Lupin Pharma (August 2022)	ENBREL (Immunex)
50	364 days	ELONOX, ELONOX HP	enoxaparin sodium	Fresenius Kabi (October 2022)	LOVENOX, LOVENOX HP (Sanofi)

No.	Approval Time	Biosimilar Name N=56	Proper Name N=17	Biosimilar Company (Approval Date)	Reference Product (Company)
51	405 days	VEGZELMA	bevacizumab	Celltrion (January 2023)	AVASTIN (Hoffmann La Roche)
52	363 days	AXBERI	enoxaparin sodium	Baxter (July 2023)	LOVENOX, LOVENOX HP (Sanofi)
53	372 days	RANOPTO	ranibizumab	Teva (October 2023)	LUCENTIS (Novartis)
54	343 days	JAMTEKI	ustekinumab	Alvotech, JAMP Pharma (November 14, 2023)	STELARA (Janssen Biotech)
55	426 days	WEZLANA	ustekinumab	Amgen Canada (December 2023)	STELARA (Janssen Inc)
56	385 days	JUBBONTI/WYOST	denosumab	Sandoz Canada (February 2024)	XGEVA/PROLIA (Amgen)

Source: [149] Biosimilars approved in Canada (smartbiggar.ca)
[a] Calculated based on the IP hold date (May 21, 2015) in Apotex's statement of claim in Court File No. T-934-16.

Table 59. Japan: PMDA Approved biosimilars [a]

No.	Product Name [JAN] N = 35	Active Substance N = 17	Therapeutic Area [b]	Authorization Date	Manufacturer/ Company Name
1	Adalimumab BS [adalimumab biosimilar 1]	adalimumab	Ankylosing spondylitis Crohn's disease Entero-Behcet's Disease Juvenile idiopathic arthritis Psoriatic arthritis Psoriasis Rheumatoid arthritis Psoriasis	29 Jun 2020	Fujifilm Kyowa Kirin Biologics
2	Adalimumab BS [adalimumab biosimilar 2]	adalimumab	Ankylosing spondylitis Crohn's disease Entero-Behcet's Disease Juvenile idiopathic arthritis Psoriatic arthritis Psoriasis Rheumatoid arthritis Psoriasis	22 Jan 2021	Daiichi Sankyo
3	Adalimumab BS MA [adalimumab biosimilar 3]	adalimumab	Ankylosing spondylitis Crohn's disease Entero-Behcet's Disease Juvenile idiopathic arthritis Psoriatic arthritis Psoriasis Rheumatoid arthritis Psoriasis	23 Mar 2021	LG Chem/ Mochida Pharmaceutical
4	Agalsidase Beta BS [JCR] [agalsidase beta biosimilar 1]	agalsidase beta	Fabry disease	28 Nov 2018	JCR Pharmaceuticals
5	Bevacizumab BS [bevacizumab biosimilar 1]	bevacizumab	Colorectal cancer	18 Jun 2019	Pfizer Japan

No.	Product Name [JAN] N = 35	Active Substance N = 17	Therapeutic Area [b]	Authorization Date	Manufacturer/ Company Name
6	Bevacizumab BS [bevacizumab biosimilar 2]	bevacizumab	Colorectal cancer	20 Sep 2019	Daiichi Sankyo
7	Bevacizumab BS [bevacizumab biosimilar 3]	bevacizumab	Metastatic colorectal cancer	27 Sep 2022	Celltrion
8	Darbepoetin alfa [KKF]	darbepoetin alfa	Anaemia	15 Aug 2018	Kyowa Hakko Kirin
9	Darbepoetin alfa (CKD-11101)	darbepoetin alfa	Anaemia	4 Dec 2018	Chong Kun Dang Pharmaceutical
10	Darbepoetin alfa BS [darbepoetin alfa biosimilar 1]	darbepoetin alfa	Anaemia	20 Sep 2020	JCR Pharmaceuticals
11	Darbepoetin alfa BS [darbepoetin alfa biosimilar 2]	darbepoetin alfa	Anaemia	20 Sep 2020	Sanwa Kagaku Kenkyusyo
12	Darbepoetin alfa BS [darbepoetin alfa biosimilar 3]	darbepoetin alfa	Anaemia	20 Sep 2019	Mylan
13	Epoetin alfa BS [epoetin alfa biosimilar 1]	epoetin alfa	Anaemia Renal anaemia	20 Jan 2010	JCR Pharmaceuticals
14	Etanercept BS [etanercept biosimilar 1]	etanercept	Juvenile idiopathic arthritis Rheumatoid arthritis	19 Jan 2018	Mochida Pharmaceutical
15	Etanercept (YLB113) [etanercept biosimilar 2]	etanercept	Juvenile idiopathic arthritis Rheumatoid arthritis	26 Mar 2019	Kyowa Pharmaceutical Industry [YL Biologics (Lupin/ Yoshindo)]
16	Filgrastim BS [filgrastim biosimilar 1]	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	21 Nov 2012	Fuji Pharma/ Mochida Pharmaceutical
17	Filgrastim BS [filgrastim biosimilar 2]	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	28 Feb 2013	Teva Pharma Japan/Nippon Kayaku
18	Filgrastim BS [filgrastim biosimilar 3]	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	24 Mar 2014	Sandoz
19	Herzuma	trastuzumab	Gastric cancer	1 Mar 2018	Celltrion/Nippon Kayaku
20	Infliximab BS (Remsima) [infliximab biosimilar 1]	infliximab	Crohn’s disease Rheumatoid arthritis Ulcerative colitis	4 Jul 2014	Celltrion/Nippon Kayaku
21	Infliximab BS (Remsima) [infliximab biosimilar 2]	infliximab	Crohn’s disease Rheumatoid arthritis Psoriasis Ulcerative colitis	27 Sep 2017	Nichi-Iko Pharmaceutical/ Yakuhan Pharmaceutical [2]

No.	Product Name [JAN] N = 35	Active Substance N = 17	Therapeutic Area [b]	Authorization Date	Manufacturer/ Company Name
22	Infliximab BS (Remsima) [infliximab biosimilar 3]	infliximab	Crohn's disease Rheumatoid arthritis Psoriasis Ulcerative colitis	2 Jul 2018	Pfizer Japan [3]
23	Insulin asS [insulin asiosimilar 1]	insulin aspart	Diabetes	23 Mar 2021	Sanofi
24	Insulin glargine BS [insulin glargine biosimilar 1]	insulin glargine	Diabetes	26 Dec 2014	Eli Lilly/ Boehringer Ingelheim [4]
25	Insulin glargine BS [insulin glargine biosimilar 2]	insulin glargine	Diabetes	28 Mar 2016	Biocon/Fujifilm Pharma [5]
26	Insulin lispro BS [insulin lispro biosimilar 1]	insulin lispro	Diabetes	25 Mar 2020	Sanofi
27	Ranibizumab BS [ranibizumab biosimilar 1]	ranibizumab	Age-related macular degeneration	27 Sep 2021	Senju Pharmaceutical
28	Rituximab BS [rituximab biosimilar 1]	rituximab	B-cell non-Hodgkin's lymphoma B-cell lymphoproliferative disorder Microscopic polyangiitis Wegener's granulomatosis	27 Sep 2017	Sandoz
29	Rituximab BS [rituximab biosimilar 2]	rituximab	B-cell non-Hodgkin's lymphoma B-cell lymphoproliferative disorder Microscopic polyangiitis Wegener's granulomatosis	20 Sep 2020	Pfizer Japan
30	Somatropin BS	somatropin	Growth hormone deficiency Turner syndrome	22 Jun 2009	Sandoz
31	Teriparatide BS [teriparatide biosimilar 1]	teriparatide	Osteoporosis	20 Sep 2019	Mochida Pharmaceutical
32	Trastuzumab BS [trastuzumab biosimilar 1]	trastuzumab	HER2+ gastric cancer	23 Mar 2018	Celltrion
33	Trastuzumab BS [trastuzumab biosimilar 2]	trastuzumab	HER2+ gastric cancer	21 Sep 2018	Daiichi Sankyo
34	Trastuzumab BS [trastuzumab biosimilar 3]	trastuzumab	HER2+ gastric cancer	21 Sep 2018	Pfizer Japan
35	Ustekinumab BS [ustekinumab biosimilar 1]	ustekinumab	plaque psoriasis psoriatic arthritis	Sep 2023	Alovotech/Fuji Pharma

Source: https://www.gabionline.net/biosimilars/general/biosimilars-approved-in-japan#:~:text=To%20date%2C%20the%20PMDA%20has,in%20Japan%2C%20see%20Table%201

[a] Data updated on 24 October 2023.
[b] Therapeutic area taken from company information, from originator product information on EMA website or from PMDA information.
JAN = Japanese Approved Name

Table 60. Australia: Biosimilars Approved in Australia, as of May 6, 2024

Active ingredient (N=15)	Reference brand (Sponsor)	Biosimilar brand (Sponsor) (N=63)	Date listed on ARTG
Epoetin lambda	Eprex® [brand of epoetin alfa] (Janssen-Cilag)	Novicrit® (Sandoz)	27/01/2010
Filgrastim	Neupogen® (Amgen)	Nivestim® (Pfizer) Tevagrastim® (Teva Pharma Australia) Zarzio® (Sandoz)	16/09/2010 29/08/2011 07/05/2013
Insulin glargine	Lantus® (Sanofi-Aventis) *Also registered under the brand names Lantus Solostar®, Optisulin®, Optisulin Solostar®, Lambeto®, Toujeo®, Toujeo SoloStar®, Toujeo Max SoloStar®*	Basaglar® (Eli Lilly Australia) Semglee® (Alphapharm)	21/11/2014 28/03/2018
Infliximab	Remicade® (Janssen-Cilag) *Also registered under the brand name Jaximab®*	Inflectra® (Pfizer) *Also registered under the brand names Remsima®, Emisima®, Flixceli®* Renflexis® (Samsung Bioepis AU)	19/08/2015 28/11/2016
Follitropin alfa	Gonal F® (Merck Serono Australia) *Also registered under the brand name Pergoveris®*	Bemfola® (Gedeon Richter) *Also registered under the brand name Afolia®*	27/11/2015
		Ovaleap® (Theramex)	10/03/2021
Etanercept	Enbrel® (Pfizer)	Brenzys®(Samsung Bioepis) Erelzi® (Sandoz) Etera® (Alphapharm) *Also registered under the brand name Rymti®*	22/07/2016 30/11/2017 01/10/2020

Active ingredient (N=15)	Reference brand (Sponsor)	Biosimilar brand (Sponsor) (N=63)	Date listed on ARTG
Adalimumab	Humira® (AbbVie)	Amgevita® (Amgen) Hadlima® (Samsung Bioepis) Hyrimoz® (Sandoz) Idacio® (Fresenius Kabi) Abrilada® (Pfizer) Hulio® (Alphapharm) Yuflyma® (Celltrion) Ciptunec® (Cipla) *Also registered under the brand name Ardalicip®*	09/11/2017 24/01/2018 01/03/2019 17/06/2020 22/02/2021 22/02/2021 25/02/2022 06/09/2022
Rituximab	MabThera® (Roche) *Also registered under the brand name Ristova®*	Riximyo® (Sandoz)	30/11/2017
		Truxima® (Celltrion), *Also registered under the brand name Ritemvia®, Rituzena®, Tuxella®*	16/04/2018
		Ruxience® (Pfizer)	03/03/2021
Trastuzumab	Herceptin® (Roche) *Also registered under the brand name Herclon®*	Herzuma® (Celltrion) *Also registered under the brand names Simabtra®, Hertuzu®* Ogivri® (Alphapharm) Ontruzant® (Samsung Bioepis) Kanjinti® (Amgen) Trazimera® (Pfizer) Trastucip® (Pfizer) *Also registered under the brand name Tuzucip®,*	17/07/2018 11/12/2018 9/01/2019 16/05/2019 19/08/2019 18/07/2022
Pegfilgrastim	Neulasta® (Amgen) *Also registered under the brand name Tezmota®, Ristempa®*	Fulphila® (Alphapharm) Neutropeg® (Accord healthcare) Ziextenzo® (Sandoz) Pelgraz® (Accord Healthcare) Filpelga® (Cipla)	17/08/2018 19/08/2019 06/09/2019 13/12/2019 19/08/2022
Bevacizumab	Avastin® (Roche)	Zirabev® (Pfizer) Mvasi® (Amgen) Abevmy® (Alphapharm) Bevaciptin® (Cipla) *Also registered under the brand name Bevacip®* Vegzelma® (Celltrion) Onbevzi® (Samsung Bioepis)	21/11/2019 30/06/2020 06/09/2021 02/11/2021 05/09/2023 24/01/2024

Active ingredient (N=15)	Reference brand (Sponsor)	Biosimilar brand (Sponsor) (N=63)	Date listed on ARTG
Enoxaparin	Clexane® (Sanofi-Aventis) *Also registered under the brand name Clexane Forte®*	Enoxapo® (Apotex) Exarane® (Juno) Exarane Forte® (Juno)	10/02/2020 28/07/2023 28/07/2023
Insulin aspart	Novomix® (Novo Nordisk) *Also registered under the brand names Novorapid®, Fiasp®*	Truvelog®, Truvelog Solostar® (Sanofi Aventis)	15/10/2020
Teriparatide	Forteo® (Eli Lilly)	Terrosa® (Gedeon Richter) Teriparatide GH® (Generic Health) Teriparatide LAPL® (Generic Health) Teriparatide LUPIN® (Generic Health) Teriparatide RBX (Sun Pharma) Teriparatide SUN (Sun Pharma) Ritosa (Sun Pharma)	01/12/2020 05/04/2023 05/04/2023 05/04/2023 02/05/2024 02/05/2024 02/05/2024
Ranibizumab	Lucentis® (Novartis)	Byooviz® (Samsung Bioepis) Raniviz® (Actor)	24/08/2022 20/12/2023
Ustekinumab	Stelara® (Janssen-Cilag)	Wezlana® (Amgen)	22/01/2024

ARTG = Australian Register of Therapeutic Goods
Data correct on 6 May 2024 per Therapeutic Goods Administration publication of the ARTG.
https://www.health.gov.au/resources/publications/biosimilar-medicines-approved-by-the-therapeutic-goods-administration?language=en

APPENDIX B: BIOSIMILAR PIPELINE

Table 61. Biosimilars in the Pipeline as of November 2023

RP	RP Proper Name	RP Manufacturer	Type	Chronic or Acute?	Biosimilar Name	Listed Biosimilar Manufacturer(s)	Status
ACTEMRA	tocilizumab	Genentech	Monoclonal Antibody - Interleukin Inhibitor	Chronic	BAT1806	Biogen–Bio-Thera	CES
					MSB11456	Fresenius Kabi	Regulatory Filing
					CT-P47	Celltrion	CES
					Tyenne	Fresenius Kabi	Pending
AVASTIN	bevacizumab	Genentech	Monoclonal Antibody - VEGF Inhibitor	Acute	SB8	Organon-Samsung	Regulatory Filing
					FKB238	AZ-Centus	Regulatory Filing
					TX16	Tanvex	PK/PD similarity
					ABEVMY	Mylan-Biocon	Regulatory Filing
					BAT1706	Bio-Thera	Regulatory Filing
					TRS003	TeRuisi	CES
					Bmab 100	Viatris	Pending
CIMZIA	certolizumab pegol	UCB	Monoclonal Antibody - TNF Inhibitor	Chronic	XCIMZANE	Xbrane-Biogen	Preclinical
COSENTYX	seckinumab	Novartis	IgG1κ Monoclonal Antibody - Binds to interleukin 17A	Chronic	BAT2306	Bio-Thera Solutions	CES
ENBREL	etanercept	Immunex	Receptor Fusion Protein - TNF Inhibitor	Chronic	YLB113	Lupin	CES
					YLB113	Lupin	CES
ENTYVIO	vedolizumab	Takeda	Monoclonal Antibody - Binds to integrin $\alpha_4\beta$	Chronic	PB016	Polpharma	CES
EYLEA	aflibercept	Regeneron	Receptor Fusion Protein - VEGF Inhibitor	Chronic	M710/MYL-1701P	Mylan-Momenta	Regulatory Filing
					FYB203	Coherus BioSciences	CES
					SB15	Biogen-Samsung	CES
					ALT-L9	Alteogen	Preclinical
					ABP 938	Amgen	CES
					SCD411	Sam Chun Dang	CES
					AVT06	Alvotech	CES
					CT-P42	Celltrion	CES
					SOK583A1	Sandoz-Hexal	CES
					Yesafili	Viatris	Pending
HERCEPTIN	trastuzumab	Genentech	Monoclonal Antibody	Acute	TX05	Tanvex	Regulatory Filing

RP	RP Proper Name	RP Manufacturer	Type	Chronic or Acute?	Biosimilar Name	Listed Biosimilar Manufacturer(s)	Status
					EG12014	Sandoz	Regulatory Filing
					HD201	Prestige Bio	CES
					HLX02 (Zercepac)	Accord BioPharma	Pending
HUMALOG	insulin lispro	Eli Lilly and Company	Insulin	Chronic	HDV INSULIN	Diasome	PK/PD similarityI
					INSULIN LISPRO, UNBRANDED	Biocon-Mylan	Preclinical
HUMIRA	adalimumab	AbbVie	Monoclonal Antibody - TNF Inhibitor	Chronic	AVT02	Alvotech-Teva	Regulatory Filing
					Amjevita HC	Amgen	CES
LANTUS	insulin glargine	Sanofi-Aventis	Insulin	Chronic	BASALIN	Gan&Lee-Sandoz	CES
					INSULIN GLARGINE	Lannett	PK/PD similarity
LUCENTIS	ranibizumab	Genentech	Monoclonal Antibody - VEGF-A Inhibitor	Chronic	XLUCANE	Xbrane-Bausch	CES
					LUBT010	Lupin	CES
NEULASTA	pegfilgrastim	Amgen	Granulocyte Colony-stimulating Factor	Acute	LAPELGA	Accord-Apotex	Regulatory Filing
					TX04	Tanvex	PK/PD similarity
					LUPIFIL-P	Lupin	Regulatory Filing
					Stimufend OBI	Fresenius Kabi	CES
NEULASTA ONPRO	pegfilgrastim	Amgen	Granulocyte Colony-stimulating Factor - On-body injector	Acute	Lupifil-P OBI	Lupin	Pending
					Udenyca OBI	Coherus	Pending
NEUPOGEN	filgrastim	Amgen	Granulocyte Colony-stimulating Factor	Acute	GRASTOFIL	Accord-Apotex	Regulatory Filing
					TX01	Tanvex	Regulatory Filing
					LUPIFIL	Lupin	PK/PD similarity
NORDITROPIN	somapacitan	Novo Nordisk	human growth hormone - Supplement	Chronic	NN8640	Novo Nordisk	CES
NOVOLOG	insulin aspart	Novo Nordisk	Insulin	Chronic	MYL-1601D	Mylan-Biocon	Regulatory Filing
					SAR341402 – SUBQ*	Sanofi	CES
					RAPILIN	Gan&Lee-Sandoz	PK/PD similarity
					INSULIN ASPARTAME HEC	Lannett	Preclinical
PERJETA	pertuzumab	Genentech	Monoclonal Antibody - Conjugate therapy	Acute	HLX11	Organon	CES
PROCRIT	erythropoietin alpha	Amgen	Erythropoiesis-stimulating Agent	Acute	APO-EPO	Apotex	CES

RP	RP Proper Name	RP Manufacturer	Type	Chronic or Acute?	Biosimilar Name	Listed Biosimilar Manufacturer(s)	Status
PROLIA	denosumab	Amgen	Monoclonal Antibody - RANKL Inhibitor	Chronic	GP2411	Sandoz-Hexal	CES
					LY06006	Luye	PK/PD similarity
					SB-16	Samsung	CES
					JHL1266	Eden	PK/PD similarity
					TVB-009	Teva	CES
					CT-P41	Celltrion	PK/PD similarity
					FKS518	Fresenius Kabi	PK/PD similarity
PROLIA/ XGEVA	denosumab	Amgen	Monoclonal Antibody - RANKL Inhibitor	Chronic	AVT03	Alvotech	CES
					BMAB-1000	Biocon	CES
					HLX14	Organon	CES
					Olimab	Intas	CES
REMICADE	infliximab	Janssen Biotech	Monoclonal Antibody - TNF Inhibitor	Chronic	NI-071	Nichi-Iko	CES
RITUXAN	rituximab	Genentech	Monoclonal Antibody - B-cell Inhibitor	Acute & Chronic	DRL RI	Dr. Reddy's	CES
					SAIT101	AZ-Archigen	CES
					MABIONCD20	Mabion	CES
SIMPONI	golimumab	Janssen Biotech	Monoclonal Antibody - TNF Inhibitor	Chronic	BAT2506	Bio-Thera	CES
					AVT05	Alvotech	Preclinical
SOLIRIS	eculizumab	Alexion	Monoclonal Antibody - C5 Protein Inhibitor	Chronic	SB12	Samsung	PK/PD similarity
					ABP 959	Amgen	CES
STELARA	ustekinumab	Janssen Biotech	Monoclonal Antibody - Interleukin Inhibitor	Chronic	FYB202	Formycon-Bioeq	CES
					NEULARA	NeuClone	PK/PD similarity
					CT-P43	Celltrion	CES
					DMB-3115	Dong-A–Meiji	CES
					BAT2206	Hikma–Bio-Thera	CES
					ABP654	Amgen	CES
					AVT04	Alvotech-Alvogen	Regulatory Filing
					SB17	Samsung	CES
					BMAB-1200	Biocon	CES
TOUJEO	insulin glargine	Sanofi-Aventis	Insulin	Chronic	INSULIN GLARGINE 300	Biocon-Mylan	Preclinical
XGEVA	denosumab	Amgen	Monoclonal Antibody - RANKL Inhibitor	Acute	RGB-14-P	Richter	CES
					LY01011	Luye	PK/PD similarity
					DENOSUMAB	Intas	PK/PD similarity

RP	RP Proper Name	RP Manufacturer	Type	Chronic or Acute?	Biosimilar Name	Listed Biosimilar Manufacturer(s)	Status
XOLAIR	omalizumab	Alexion	Monoclonal Antibody - IgE Inhibitor	Chronic	CT-P39	Celltrion	PK/PD similarity
					GBR 310	Glenmark	PK/PD similarity
					BP11	Aurobindo	PK/PD similarity
					TEV-45779	Teva	CES
					ADL-018	Kashiv Biosciences	CES

Sources: (Cardinal Health, 2023); (Cencora, Nov. 2023)

APPENDIX C: INDIVIDUAL BIOSIMILAR PRODUCT MARKET SHARE PARAMETERS

Market	Product	Entry Order	Functional Form	Parameter	Estimate (95% CI)	Standard Error	t Value	p Value	Model Efron R Squared	Model SSE	Model AIC
Bevacizumab (Avastin)	Mvasi	1	Exponential decay	b_{max}	0.539 (0.500, 0.577)	0.019	28.83	<0.001	0.958	0.0844	-101.8
Bevacizumab (Avastin)	Mvasi	1	Exponential decay	C	0.354 (0.162, 0.546)	0.094	3.76	<0.001	0.958	0.0844	-101.8
Bevacizumab (Avastin)	Mvasi	1	Exponential decay	D	2.583 (1.379, 3.788)	0.590	4.38	<0.001	0.958	0.0844	-101.8
Bevacizumab (Avastin)	Zirabev	2	Logistic growth	b_{max}	0.389 (0.354, 0.423)	0.017	22.96	<0.001	0.958	0.0844	-101.8
Bevacizumab (Avastin)	Zirabev	2	Logistic growth	K	0.272 (0.104, 0.441)	0.082	3.30	0.002	0.958	0.0844	-101.8
Bevacizumab (Avastin)	Zirabev	2	Logistic growth	T	0.916 (0.724, 1.109)	0.094	9.73	<0.001	0.958	0.0844	-101.8
Filgrastim (Neupogen)	Nivestym	2	Logistic growth	b_{max}	0.328 (0.270, 0.387)	0.029	11.37	<0.001	0.967	0.1469	-119.8
Filgrastim (Neupogen)	Nivestym	2	Logistic growth	K	0.768 (0.276, 1.261)	0.244	3.16	0.003	0.967	0.1469	-119.8
Filgrastim (Neupogen)	Nivestym	2	Logistic growth	T	1.847 (1.283, 2.411)	0.279	6.62	<0.001	0.967	0.1469	-119.8
Filgrastim (Neupogen)	Zarxio	1	Exponential decay	b_{max}	0.629 (0.513, 0.744)	0.057	11.01	<0.001	0.967	0.1469	-119.8
Filgrastim (Neupogen)	Zarxio	1	Exponential decay	C	0.170 (0.036, 0.303)	0.066	2.58	0.014	0.967	0.1469	-119.8
Filgrastim (Neupogen)	Zarxio	1	Exponential decay	D	1.731 (0.660, 2.802)	0.530	3.27	0.002	0.967	0.1469	-119.8
Infliximab (Remicade)	Avsola	3	Logistic growth	b_{max}	0.201 (0.079, 0.323)	0.061	3.32	0.002	0.981	0.0936	-185.7
Infliximab (Remicade)	Avsola	3	Logistic growth	K	0.531 (-0.103, 1.165)	0.316	1.68	0.099	0.981	0.0936	-185.7
Infliximab (Remicade)	Avsola	3	Logistic growth	T	1.241 (0.300, 2.182)	0.468	2.65	0.011	0.981	0.0936	-185.7
Infliximab (Remicade)	Inflectra	1	Exponential decay	b_{max}	0.531 (0.409, 0.654)	0.061	8.71	<0.001	0.981	0.0936	-185.7
Infliximab (Remicade)	Inflectra	1	Exponential decay	C	0.322 (0.201, 0.443)	0.060	5.34	<0.001	0.981	0.0936	-185.7
Infliximab (Remicade)	Inflectra	1	Exponential decay	D	1.042 (0.688, 1.396)	0.176	5.92	<0.001	0.981	0.0936	-185.7
Infliximab (Remicade)	Renflexis	2	Logistic growth	b_{max}	0.267 (0.245, 0.290)	0.011	23.56	<0.001	0.981	0.0936	-185.7
Infliximab (Remicade)	Renflexis	2	Logistic growth	K	0.277 (0.081, 0.473)	0.098	2.84	0.007	0.981	0.0936	-185.7
Infliximab (Remicade)	Renflexis	2	Logistic growth	T	0.927 (0.703, 1.150)	0.111	8.34	<0.001	0.981	0.0936	-185.7
Pegfilgrastim (Neulasta)	Fulphila	1	Exponential decay	b_{max}	0.260 (0.222, 0.298)	0.019	13.68	<0.001	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Fulphila	1	Exponential decay	C	4.771 (-1.616, 11.158)	3.192	1.49	0.140	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Fulphila	1	Exponential decay	D	1.380 (0.195, 2.565)	0.592	2.33	0.023	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Nyvepria	4	Logistic growth	b_{max}	0.092 (0.043, 0.142)	0.025	3.73	<0.001	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Nyvepria	4	Logistic growth	K	0.108 (-0.614, 0.830)	0.361	0.30	0.766	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Nyvepria	4	Logistic growth	T	0.242 (-0.471, 0.955)	0.356	0.68	0.500	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Udenyca	2	Harmonic oscillator growth	b_{max}	0.459 (0.390, 0.528)	0.034	13.37	<0.001	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Udenyca	2	Harmonic oscillator growth	a	1.020 (-1.035, 3.076)	1.027	0.99	0.325	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Udenyca	2	Harmonic oscillator growth	c	1.022 (-1.203, 3.247)	1.112	0.92	0.362	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Udenyca	2	Harmonic oscillator growth	d	0.575 (-0.589, 1.739)	0.582	0.99	0.327	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Udenyca	2	Harmonic oscillator growth	f	1.208 (1.042, 1.374)	0.083	14.54	<0.001	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Udenyca	2	Harmonic oscillator growth	g	-1.500 (-1.647, -1.353)	0.074	-20.39	<0.001	0.881	0.3945	-149.6

Market	Product	Entry Order	Functional Form	Parameter	Estimate (95% CI)	Standard Error	t Value	p Value	Model Efron R Squared	Model SSE	Model AIC
Pegfilgrastim (Neulasta)	Ziextenzo	3	Harmonic oscillator growth	b_{max}	0.191 (0.145, 0.236)	0.023	8.40	<0.001	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Ziextenzo	3	Harmonic oscillator growth	a	-0.248 (-14.335, 13.839)	7.040	-0.04	0.972	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Ziextenzo	3	Harmonic oscillator growth	c	0.386 (-6.481, 7.253)	3.432	0.11	0.911	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Ziextenzo	3	Harmonic oscillator growth	d	8.331 (-62.948, 79.61)	35.622	0.23	0.816	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Ziextenzo	3	Harmonic oscillator growth	f	0.321 (-33.992, 34.635)	17.148	0.02	0.985	0.881	0.3945	-149.6
Pegfilgrastim (Neulasta)	Ziextenzo	3	Harmonic oscillator growth	g	2.421 (-61.674, 66.515)	32.031	0.08	0.940	0.881	0.3945	-149.6
Rituximab (Rituxan)	Riabni	3	Logistic growth	b_{max}	0.107 (0.072, 0.142)	0.017	6.23	<0.001	0.953	0.1227	-140.6
Rituximab (Rituxan)	Riabni	3	Logistic growth	K	0.348 (-0.350, 1.047)	0.346	1.01	0.320	0.953	0.1227	-140.6
Rituximab (Rituxan)	Riabni	3	Logistic growth	T	1.364 (0.555, 2.172)	0.401	3.40	0.001	0.953	0.1227	-140.6
Rituximab (Rituxan)	Ruxience	2	Logistic growth	b_{max}	0.410 (0.383, 0.436)	0.013	31.08	<0.001	0.953	0.1227	-140.6
Rituximab (Rituxan)	Ruxience	2	Logistic growth	K	0.118 (0.023, 0.213)	0.047	2.50	0.017	0.953	0.1227	-140.6
Rituximab (Rituxan)	Ruxience	2	Logistic growth	T	0.365 (0.248, 0.481)	0.058	6.33	<0.001	0.953	0.1227	-140.6
Rituximab (Rituxan)	Truxima	1	Exponential decay	b_{max}	0.483 (0.455, 0.511)	0.014	35.05	<0.001	0.953	0.1227	-140.6
Rituximab (Rituxan)	Truxima	1	Exponential decay	C	1.713 (0.799, 2.626)	0.453	3.78	<0.001	0.953	0.1227	-140.6
Rituximab (Rituxan)	Truxima	1	Exponential decay	D	2.604 (1.176, 4.032)	0.708	3.68	<0.001	0.953	0.1227	-140.6
Trastuzumab (Herceptin)	Herzuma	4	Logistic growth	b_{max}	0.018 (0.000, 0.036)	0.009	2.03	0.047	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Herzuma	4	Logistic growth	K	0.419 (-1.820, 2.659)	1.118	0.38	0.709	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Herzuma	4	Logistic growth	T	0.555 (-1.600, 2.710)	1.076	0.52	0.608	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Kanjinti	1	Exponential decay	b_{max}	0.397 (0.361, 0.433)	0.018	22.02	<0.001	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Kanjinti	1	Exponential decay	C	0.324 (0.279, 0.368)	0.022	14.59	<0.001	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Kanjinti	1	Exponential decay	D	1.831 (1.580, 2.083)	0.126	14.59	<0.001	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Ogivri	2	Logistic growth	b_{max}	0.160 (0.134, 0.187)	0.013	12.17	<0.001	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Ogivri	2	Logistic growth	K	0.704 (0.245, 1.162)	0.229	3.07	0.003	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Ogivri	2	Logistic growth	T	0.696 (0.298, 1.094)	0.199	3.51	<0.001	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Ontruzant	5	Logistic growth	b_{max}	0.144 (0.104, 0.184)	0.020	7.20	<0.001	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Ontruzant	5	Logistic growth	K	0.409 (0.139, 0.679)	0.135	3.03	0.004	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Ontruzant	5	Logistic growth	T	1.913 (1.528, 2.297)	0.192	9.97	<0.001	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Trazimera	3	Logistic growth	b_{max}	0.281 (0.264, 0.298)	0.008	33.87	<0.001	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Trazimera	3	Logistic growth	K	0.278 (0.188, 0.368)	0.045	6.16	<0.001	0.995	0.0228	-339.6
Trastuzumab (Herceptin)	Trazimera	3	Logistic growth	T	0.968 (0.864, 1.073)	0.052	18.58	<0.001	0.995	0.0228	-339.6

CI = confidence interval; SSE = sum of squared errors; AIC = Akaike information criterion

Note: Table shows fitted growth functions, which model the uptake of market share that individual biosimilars earn in their respective biosimilar markets. We define a biosimilar market to include only the biosimilar products without their RP. Table only includes the six U.S. markets with at least two biosimilars each with at least two years of sales data. Market share is calculated from net sales, which are estimated using volume sales data from IQVIA NSP and pricing data from both IQVIA NSP and CMS ASP pricing files.