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Pharmer's Market: How Biosimilars are Shaking Up the Pharmaceutical Landscape

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Pharmer's Market:

How Biosimilars are Shaking Up the Pharmaceutical Landscape

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Abstract

In such a divisive political climate, there are few issues that have bipartisan support in the US; however, both parties agree it is time to tackle sky-high drug prices. Pharmaceutical prices in the US continue to increase every year with many drugs known as biologics leading the way. As innovation continues, biologics are becoming a larger proportion of the drug market, and they represent some of the most expensive treatments. Nevertheless, there is little competition in these markets from biosimilars, which are like generic versions of biologics that can drive prices down. In this thesis, I examine the association between the entrance of biosimilars in the US and following changes in quantity of the biologics. I find that biosimilar entrance into the market is related to large decreases in utilization for biologics and that biosimilars in the US tend to penetrate faster than estimates in Europe but slower than what is seen in the US generic market. With these results, I estimate that potential savings due to biosimilars could be $29 billion USD over the next ten years with the capacity to be seven times greater if future policies properly incentivize biosimilar competition.

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1. Introduction

As US healthcare expenditures continue to rise exponentially, many are looking to the pharmaceutical industry as a place to cut costs. Lower drug prices are a constant topic and priority for lawmakers: there have been four congressional hearings about drug pricing since the new Congress took office, and President Donald Trump vowed to tackle pharmaceutical costs in his most recent State of the Union address (Facher, 2019; Imbert, 2019). Recent statistics show that healthcare costs grew 3.9% and were 17.3% of our GDP in 2017, and the Centers for Medicare and Medicaid Services (CMS) notes that pharmaceutical costs equaled approximately $333 billion that year (Centers for Medicare & Medicaid Services, 2018; Yu, Atteberry, & Bach, 2018). Although there are many ways to address rising pharmaceutical costs, one potential place for savings is the expanding market for biologics and biosimilars, which represents 38% of US drug spending and 70% of growth in drug spending in 2017, even though they are used by only 1-2% of the population (Mulcahy et al., 2018).

Unlike most small molecule drugs such as Advil, Claritin, and penicillin antibiotics that are chemically synthesized (made entirely of known chemical compounds), biologics are products such as vaccines, gene therapy, and allergenics that are composed of biological material (sugars, proteins, nucleic acids, cells). The process of synthesizing biologics is more intensive than chemically derived compounds, which makes biologics extremely susceptible to contamination and other human errors (FDA, 2018). Because this process is so complex, it is difficult to create exact replicates of biologics compared to conventional drugs once the patent of the reference biologic expires (there are sometimes even variations among batches of the drug) (Vulto &

Jaquez, 2017). These factors along with high start-up costs and US regulations have led to few entries of biosimilars, or "generic" versions of name brand biologics (Grabowski et al., 2014).

Because biosimilars are just starting to enter the US market (many have been on the market for fewer than two years), there is little research analyzing the impact of biosimilars on the US pharmaceutical industry. However, it is crucial to understand the economic impacts and incentive structure surrounding the entrance of biosimilars because many reference biologics will be going off patent over the next decade. This market is instrumental in addressing rising costs, and even the Food and Drug Administration (FDA) recognizes its importance. For example in March of 2019, FDA Commissioner, Scott Gottlieb, announced a new policy for biosimilars noting, "We're at a critical point for the future of biosimilars in the US. Millions of American patients stand to benefit from increased utilization of these lower-cost, high-quality products," and in other statements, he has reported that the FDA is working on "a dozen policies" surrounding biosimilars (Davio, 2018; Gottlieb, 2019). In addition, biologics are also the product of cutting edge research: an example includes drugs used for immunotherapy, in which the body's immune system is boosted to fight off cancer (Levy & Stump-Sutliff, n.d.). Thus as innovation continues, biologics and biosimilars may become an even larger portion of the pharmaceutical market, and it is becoming increasingly important to understand their market behavior and impact on the pharmaceutical industry.

In this thesis, I expand the number of biosimilars previously studied to explore the relationship between biosimilar entry and subsequent changes in quantity to the reference biologic on the US market. I use monthly pharmaceutical private insurance claims data

from 2006-2018 on four biosimilars and their reference biologics to examine drops in reference biologic utilization upon biosimilar entry and how fast these biosimilars penetrate the market. My analysis suggests that biosimilars are adopted faster than estimates from Europe over the last decade but slower than measurements in the US generic market. These results provide insight into future policy reforms aimed at increasing competition and uptake, which may lead to lower drug costs, expanded access, and enormous savings.

2. Background

2.1 *The Science of Biosimilars*

Naming conventions in the market for biologics is slightly different from those used in the small molecule or chemically synthesized drug market. For example, biologics can be separated into several drug classes, and each drug class contains the reference biologic that has a brand name and the biosimilars that also have separate product names. For example, one of the first biosimilars in the US market is named Zarxio. It is a biosimilar of the reference product/biologic Neupogen, and it is a part of the drug class filgrastim. For simplicity, this paper uses the drug class name followed by (R) for the reference product and (S) for the biosimilar(s). An example includes filgrastim (R) for Neupogen and filgrastim (S) for Zarxio. Meanwhile in the conventional drug market, there is a brand name for the small molecule and a single generic name for all generics. For example, Motrin is a brand name for ibuprofen, which is the generic name for all companies selling copies of Motrin.

The science behind biosimilars is also different from chemically synthesized drugs. Unlike generics and name brand small molecules, biosimilars are not exact copies of reference biologics, so many in the healthcare profession worry about the safety and efficacy of biosimilars. In particular, patients question whether it is safe to switch from the reference biologic to the cheaper biosimilar once it comes onto the market. To alleviate this concern, a two-year study on infliximab followed two groups of patients: one that took only the reference biologic and the other that took the reference biologic for the first year and then switched to the biosimilar for the second. By analyzing frequencies of adverse events, antidrug antibodies, and other biological tests, this study showed that switching to infliximab (S) is "not associated with any detrimental effects on efficacy, immunogenicity or safety" (Yoo et al., 2017). There have also been randomized control trials showing that groups taking the biosimilar and reference biologic tend to have similar outcomes for filgrastim products, which further highlights that biosimilars are safe (Botteri et al., 2018). In addition, Cohen and coauthors reviewed multiple biosimilar switching studies to find that there "is a low risk of either safety concern or loss of efficacy after switching to a biosimilar" (2018).

2.2 *US Approval Process for Biosimilars*

US regulation surrounding biologics is relatively lacking compared to the policies addressing the chemically synthesized or small molecule market. Thus, many regulatory policies aimed at increasing competition in the pharmaceutical industry do not apply to biosimilars and their reference biologics. For example, the Hatch-Waxman Act passed in 1984 was enacted in response to high costs of drugs, and it delineated a shorter approval

process in which generic drugs only had to prove "bioequivalence" (generic drug is the exact same chemical compound of name brand drug). This saved both time and money, as generics no longer have to go through lengthy and expensive clinical trials to get to market. Past research has shown the many effects of Hatch-Waxman such as increased competition in the drug market, which resulted in lower prices and expanded access to drugs (Grabowski et al., 2011).

However unlike chemically synthesized therapeutics, biologics and biosimilars are not protected by the Hatch-Waxman Act due to the difficulty of creating a "bioequivalent" biosimilar. Because of this criteria and the science of biologic drugs, biosimilars did not have a separate and defined process to get FDA approval like generic drugs (until 2010). Thus to get to market, biosimilars were required to complete the approval process like all new drugs. However unlike new drugs, biosimilars do not necessarily have patents because they are not innovative products; therefore, they do not have an exclusivity period in which they can monopolistically set prices. Given the high costs of research and development, biosimilars were not incentivized to enter the market. Because of this problem, Congress included a provision in the 2010 Affordable Care Act known as the Biologics Price Competition and Innovation Act (BPCIA) that mandated that the FDA delineate a shorter pathway for biosimilar approval. In this approval plan, the FDA requires "biosimilarity" in which the biosimilar must have "no clinically meaningful difference…[from] the reference product in terms of safety, purity, and potency." To meet this criteria, biosimilars must complete shortened clinical trials and various analyses, which results in greater start-up costs compared to those for chemically

synthesized generic drugs. After these analyses are complete, the FDA can approve the biosimilar for use in the US market.

2.3 *Current Research on Biosimilars*

Although there is not extensive research on biosimilar entry in the US, there has been some research in Europe, as the first biosimilar entered the European market in 2006 (Scott Morton et al., 2018). In their paper, Scott Morton and co-authors analyze the relationship between public polices in European countries to biosimilar entry, price, and penetration for three drug classes of biologics: epoetin, filgrastim, and somatropin. Their research finds that the prices of biologics decrease on average by 3.5% and penetration increases by 5.5% per year after biosimilar entry; however, these effects are primarily driven by epoetin and fligrastim. They also find that biosimilar entry and prices are negatively correlated, indicating that drug prices potentially influence the decision to enter the market. The authors also estimate that between 2006-2015, the biosimilars of these three drug classes generated a savings of $1.5 billion US dollars in Europe (Scott Morton et al., 2018).

Because of perverse incentives for biosimilars to enter the market before the BPCIA was passed in 2010, research on the effects of biosimilar entry to the US market is limited in scope. In fact, the first biosimilar to be approved via the BPCIA happened in 2015. Thus, past research predicts potential savings with little economic analysis and evidence, and recent literature explores the cost savings associated with only one drug class: filgrastim (Mulcahy et al., 2018). Mulcahy and coauthors find that the market share for filgrastim (S) has increased over time, and they use this to project savings of $54

billion over the next ten years due to all biosimilar entry. However, the authors highlight that they made large assumptions to calculate this estimate, resulting in a lower bound of $24 billion and an upper bound of $150 billion For example, they did not factor in the growth in demand of the drug due to lower prices (2018). In addition, since there was heterogeneity in the effects of biosimilar entry in Europe, basing this calculation on one drug class (filgrastim) seems questionable (Scott Morton et al., 2018).

2.4 *Landscape of the Biologic and Biosimilar Market*

When looking at the market for biosimilars, many compare it to the US market for generics. The two markets have many similarities: biosimilars and generics are both derivatives of original products, are able to enter the market only after the patent of the original product expires, and aim to offset high pharmaceutical prices through increased competition. Previous research by Scott Morton on the pharmaceutical industry adapts basic economic models to the market for generics (1999). This research demonstrates that generics are more likely to enter the market the greater the revenue for the reference drug, the lower the fixed and sunk costs, and if the drug treats a chronic condition. Thus, drugs with larger markets are likely to experience more generic competition, which would then result in lower prices (Scott Morton, 1999). Based on this experience, I expect that the entrance of biosimilars should be competitive, as the US market size for biologics was estimated to be $120 billion in 2017, with one biologic, Humira, generating over $12 billion in revenue in 2017 (Abbvie, 2018; IQVIA Institute for Human Data Science, 2018). In addition, recent estimates in the generic market have found that market share for the name brand drug falls to 12% after one year of the generic being on the market,

and that generics make up approximately 86% of prescriptions resulting in a cost savings of over $1.5 trillion over the past 10 years (Grabowski et al., 2016; Thayer, 2014). Due to evidence and research in the generic market, I expect that when a biosimilar enters the market, the increased competition has the potential to result in large changes in price and quantity in the market for the reference biologic.

Although the generic market is comparable to the US biosimilar market, there are four key differences. The first is that the science of biosimilars and generics is different. Generic drugs are exact copies of name brand products, while biosimilars are only "highly similar" to the reference product. In addition, generic drugs and chemically synthesized compounds tend to be much smaller and well-defined, while biologic drugs are larger molecules "derived from living material" (FDA, 2015). Because these drugs are not identical, they may not be considered perfect substitutes, which may affect their behavior in the market.

The second difference is that the FDA has two classifications of biosimilars: an approved biosimilar and an interchangeable biosimilar, while there is only one type of generic. Currently, none of the FDA approved biosimilars in the US satisfy the "interchangeability" requirement, which is potentially due to the additional clinical trials and tests estimated to cost $100-200 million that must be completed to achieve this status (GlobalData Healthcare, 2018; Ramakrishnan & Ching, 2018). This is unlike the generic market because most name brand small molecules can be interchanged for generics by the pharmacist without interference from a physician. However in the biologics market, a patient may only receive the biosimilar if the physician specifically prescribes it. This will perhaps distort incentives and the substitutability of biosimilars, as it signals to

consumers that a biosimilar is not "the same". Meanwhile in Europe, the EMA does not have this interchangeability requirement and allows countries determine whether biosimilars can be substituted (Ramakrishnan & Ching, 2018).

Another potential barrier to biosimilar adoption is the US patent system. Compared to Europe, there has been stronger patent litigation in the US surrounding reference biologics (Megerlin et al., 2013). For example in the US, some biosimilars choose to go through what is known as a "patent dance" in which they reveal their biosimilar application with the reference product manufacturer. This often results in delays of biosimilar approval and the disclosures of sensitive information (Sarpatwari et al., 2018). In addition, patent challenges have kept many approved biosimilars off the US market, as manufacturers cover their biologic drugs with "patent thickets". For example, two reference biologics, Humira and Remicade, are covered by over 100 patents while most conventional drugs usually have about a dozen patents (Koons, 2017). This large number of patents allows drugs like Humira to have a greater period of market exclusivity with monopolistic power even though their main patent covering the science of the drug has already expired. Because these drugs are so expensive and lucrative, pharmaceutical companies are also potentially willing to fight incoming competitors, which prevents biosimilar entry while these lawsuits take place.

In addition to strong patent protection and intense patent litigation for reference biologics, listed biosimilar prices are different compared to those normally seen in the generic market. While generic prices often offer 80% savings compared to name brand drugs, biosimilar list price savings are modest and range from 15-35% (Florko & Silverman, 2018). However, actual cost savings of biosimilars could vary depending on

rebates made by the reference biologic manufacturer trying to maintain its market share. Many biosimilar manufacturers argue that they cannot offer steep discounts because their startup costs are greater than traditional generic drugs due to the requirement of some clinical trials, which makes it difficult to recoup their investments. In fact, estimates indicate that it takes approximately $1-4 million to develop a generic drug, but $100-250 million for a biosimilar (Blackstone & Joseph, 2013). Biosimilar manufacturers also have to spend money marketing their drug, as patients and physicians seem to be more wary of adopting biosimilars compared to generics (Forsyth & McClearn, 2018). In addition, many pharmaceutical companies offer rebates to insurers for these expensive reference biologics conditional on exclusivity. Thus, insurers cannot cover biosimilars unless they are willing to forgo the rebate, which further disincentives insurers from adding biosimilars to their formularies (Sarpatwari et al., 2018).

As of December 2018, there are eight biosimilars of six drug classes sold on the US market. Figure A and Table 1 provide information on selected biologics currently sold on the US market. Filgrastim is used to treat neutropenia, which is low white blood cell count usually due to cancer, chemotherapy, and bone marrow transplants, and two biosimilars of this drug class that are currently being sold on the market include Nivestym and Zarxio. Infliximab is used to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. It also has two biosimilars on the US market: Renflexis and Inflectra. Pegfilgratim is used to decrease the risk of infection that might result from chemotherapy treatments, and its biosimilar is Fulphila. The final biosimilar approved via the BPCIA on the market is Retacrit. This is a biosimilar of epoetin alfa that is used to treat anemia caused by

chronic kidney disease. There are also an additional two biosimilars approved via the 505 (b) 2[1] pathway instead of the guidelines under the BPCIA. These are Basaglar and Omnitrope, which are biosimilars for insulin glargine and somatropin resepectively. Under the 505 (b) 2 pathway, these drugs are "not strictly generics, but are often not entirely novel new molecular entities" (Chandanais, 2017). Thus, we expect that there may be differences in the way that these two drugs behave in the market. Insulin glargine is used to treat diabetes, while somatropin indications include growth hormone deficiency, idiopathic short status, Turner Syndrome and Prader-Willi Syndrome.

My thesis adds to the current literature by expanding the number of biosimilars and drug classes that are analyzed in the US. Current literature in the US only explores one drug class; however, there are more that have been approved by the FDA, and I explore four drug classes (Mulcahy et al., 2018). In addition, studies in Europe analyzed only three drug classes of biologics, yet there have been several additional biosimilars to enter the market since then. Although not all of the biosimilars approved in the US are on the US market, there are, to my knowledge, an additional seven (Inflectra, Renflexis, Nivestym, Basaglar, Omnitrope, Fulphila, Retacrit) that are currently being sold that have not been analyzed (Cohen, 2018; Davio, 2018; DiGrande, 2018; Eli Lilly and Company, 2016; The Center for Biosimilars, 2018). Using claims data, I analyze the association between biosimilar entrance and reference biologic market share and quantity changes for three additional biosimilars compared to previous research. The analysis of these additional drugs allows updated calculations and possibly better estimates of potential future savings. In addition, this thesis may provide insights on the incentives driving the

[1] The 505 (b) 2 pathway is a hybrid between a full, new drug application and an abbreviated new drug application. Before the BPCIA, the FDA approved a few selected biosimilars via 505 (b) 2.

biologics market, as some biosimilars are approved through different pathways and others have varying market sizes.

3. Conceptual Framework

Economic theory suggests that rational consumers should pick the cheaper of two goods if they are perfect substitutes. Thus, when a less expensive alternative comes onto the market, it should capture some of the surplus and potentially expand the market. Because a biosimilar is "highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product," I expect the reference biologic and the biosimilar to behave as substitutes (FDA, 2017). Therefore when the biosimilar enters the market, I expect the utilization of the reference biologic to decrease.

The adoption of biosimilars is dependent on a few key players: the FDA, pharmaceutical companies, insurers, patients, physicians, and in some cases pharmacy benefit managers (PBMs). In order for a biosimilar to first get to market, it must be approved by the FDA. In addition, the biosimilar must also wait to enter the market until the patents for the reference biologic expire, and currently many reference product manufacturers create "patent thickets" around their reference biologic to deter biosimilar entry (Loftus & Roland, 2018). Once the biosimilar has entered the market, pharmaceutical companies may sell their products directly to hospitals and/or insurers, or they may sell them through PBMs. These insurers then must decide whether they would like to cover biosimilars, and then physicians must determine whether or not they would like to prescribe it to patients.

Because of the many players involved in getting biosimilars to patients, there are several potential barriers to biosimilar adoption, as each player has the ability to impede biosimilar take-up. For example, there is imperfect and asymmetric information at multiple levels: patients and physicians do not often see the costs of reference biologics or biosimilars, insurers cannot observe the rebates received by pharmacy benefit managers, and these insurers do not know the actual cost to make the drug incurred by the pharmaceutical companies. In addition, this imperfect information may also lead to moral hazard, as patients do not absorb the entire cost of the reference biologic or biosimilar. The market also potentially suffers from inertia or status quo bias, as many patients and physicians do not care to switch from a reference biologic to biosimilar if they have already been on the reference biologic.

4. Data

Because I assume that the reference biologic and biosimilar will behave as substitutes, I use pharmacy claims data to understand utilization trends before and after the biosimilar enters the market and compare this to the European biosimilars market and the US generic market. To probe into the relationship between biosimilars and their reference biologic and how fast biosimilars penetrate the market, data come from two different sources. These sources provide a landscape of the biologic market in the US and Europe and provide private insurance claims of each of the biosimilars currently on the US market. The first data source provides information on biologics approved in Europe and the US from 2006-2018 to establish which biologics and biosimilars are used in the analysis and are available in the US. The second data source contains private

pharmacy claims for the reference biologic and biosimilar drugs currently sold on the US market.

The first data source comes from various governmental regulatory agencies and pharmaceutical company websites and is a compiled list of all the biosimilars in the US and Europe that have either been approved by the US Drug Administration (FDA) or the European Medicines Agency (EMA). For each biosimilar, this list includes the date of EMA and/or FDA approval, the reference product, drug class, US market entry date, and US patent expiration date. This list includes a total of 45 biosimilars of 15 biologic drug classes. Of these 45 biosimilars, four have received FDA approval, 28 have EMA approval, and 13 have both (Figure A). A list of the biosimilars in the US, their names, and other key information is included in Table 1. Out of the biosimilars approved in the US, eight are currently being sold on the market and they represent a total of six biologic drug classes: filgrastim, pegfilgrastim, epoetin alfa, infliximab, insulin glargine, and somatropin. However, I only have data on four of these drug classes: filgrastim, infliximab, insulin glargine, and somatropin.

When using these data, I encounter problems because of the varying patent expiration dates, as some drugs are currently tied up in litigation while others have had extensions or modified their original patents to increase the period of market exclusivity. For example, there are two drug classes whose names are filgrastim and pegfilgrastim that are almost identical and treat the same indications. The only difference between the two is a slight change in the chemical structure that allows pegfilgratim to stay in the body longer. This list is also not a comprehensive list of all the biologics; it includes

those that have biosimilars in either Europe or the US, thus there could be other biologic drugs or biosimilars approved in other countries.

The second source is the Optum Dataset, which contains private insurance claims from United Healthcare and has information on pharmacy utilization, pharmacy claim costs, and patient characteristics. This data source provides monthly aggregates of healthcare claims from to 2006-2018, which captures the entry of somatropin (s). (Somatropin was the earliest biosimilar on the market in the US in 2007.) I use this data source on private claims because it has monthly data instead of yearly data, and many of the drugs have entered the market so recently that it is difficult to find public data.

Data from Optum is relatively limited in scope due to patient sensitivity. For example, I do not have individual claims data; I only have monthly aggregates. Thus, I have information on the number of claims for a particular drug in a given month. Although there are eight biosimilars on the market, this dataset only contains claims for four (See note under Figure A). However, I assume that there were no claims for these drugs during the time period I am currently analyzing because two additional biosimilars for the drug classes filgrastim and infliximab were on Optum's internal list of drugs, and the other two just recently entered the market. This assumption seems reasonable because utilization rates for one of the references products is already low while the other biosimilar just entered the market in October 2018. In addition, due to privacy reasons, the number of claims is censored for a drug if it is below 10, which may impact my results for biologic drugs that have lower utilization rates.

5. Methodology

In this thesis, I examine both changes in market share and quantity upon biosimilar market entry. Regressions 1-2 analyze quantity (number of prescriptions), and regressions 3-4 look at market share. To examine the association between biosimilar market entry and changes in quantity for the reference biologic, I pool all the data on four drug classes in OLS regression **(1)**, where D is equal to one if a biosimilar for reference biologic *i* is being sold on the market in month *m* of year *t*, Y_{imt} is the number of claims or log of the number of claims for the reference biologic, λ_t are year fixed effects, and φ_i are drug fixed effects. By using drug fixed effects, I control for time-invariant factors related to the market and diseases in which the drug treats. In regression (1), I am most interested in the estimate of β_1, as it illustrates the predictive effect of biosimilar entrance on utilization of reference biologics for the overall market.

$$Y_{imt} = \beta_0 + \beta_1(D_{imt}) + \lambda_t + \varphi_i + \varepsilon_{imt} \quad \textbf{(1)}$$

To understand the relationship between biosimilar market entry and changes in quantity for individual drug classes, I run related regression **(2)** four times (one for each drug class)**,** where D is equal to one if a biosimilar for reference biologic is being sold on the market in month *m*, and Y_m the number of claims or log number of claims for the reference biologic in month *m*.[2] I also run regression **(2)** with a time lag on the dummy variable indicating when the biosimilar is available at six, twelve, eighteen, and twenty-four months to understand when significant biosimilar adoption begins. I am most interested in the estimate of γ_1, as it illustrates the relationship between biosimilar

[2] Results for regression 2 with year fixed effects are included in the Appendix, and a detailed discussion on why they are excluded in the main results is in the results section.

entrance and changes in the reference biologic utilization for each individual drug class, allowing me to see heterogeneity among drugs.

$$Y_m = \gamma_0 + \gamma_1(D_m) + \gamma_2(D_{m-6}) + \gamma_3(D_{m-12}) + \gamma_4(D_{m-18}) + \gamma_5(D_{m-24}) + \varepsilon_m \quad \textbf{(2)}$$

In addition, I use regression **(3)** to examine monthly market share decline of the reference biologic over time, where X_{imt} is the number of months the biosimilar has been available on the market in month *m* of year *t*, the dependent variable is the market share of the reference biologic in month *m* of year *t*, λ_t is year fixed effects, and φ_i is drug fixed effects. The estimate of δ_1 will shed light on how fast the biosimilar is being adopted when it enters the market. Using similar methods to Scott Morton and coauthors (2018), market share is calculated by summing the number of prescriptions for reference biologic in drug class *i* sold in month *m* of year *t* and dividing it by the total number of prescriptions for the biosimilar(s) and its reference biologic in drug class *i* for that same month.

$$Marketshare_{imt} = \delta_0 + \delta_1(X_{imt}) + \lambda_t + \varphi_i + \varepsilon_{imt} \quad \textbf{(3)}$$

I then repeat a similar regression to analyze market share decline and penetration rates for each of the four drug classes. I run regression **(4)** for each drug class (four times), where X_m is the number of months the biosimilar has been on the market in month *m*, and the dependent variable is the market share of the reference biologic in month *m*. With this regression, the estimate of ϕ_1 will indicate the market share decline of the reference biologic or the monthly penetrance of the biosimilar.

$$Marketshare_m = \phi_0 + \phi_1(X_m) + \varepsilon_m \quad \textbf{(4)}$$

In addition, I run regression (1) with the dependent variable being market share for each reference biologic to provide insight into the market share that is captured by each

biosimilar when it enters the market. I then use these results to project rough estimates on cost savings due to predicted market entry of biosimiliar products over the next ten years. For the regressions **(1)** and **(2)**, I also create a dummy variable indicating FDA approval as a control with results shown in the Appendix. However, this dummy variable is not reported in the main findings, as I believe biosimilar entrance is the driver in changes in utilization, not FDA approval.[3]

6. Results

Results from regression (**1)** are shown in Table 2 and Table 3. The coefficients are significant and negative, which indicates that in the overall biologics market, biosimilar entrance is associated with a decrease in the number of claims for the reference product. Results that separate the drug classes in regression **(2)** are reported in Table 4 and Table 5. In three of the four biologic drug classes, the number of prescriptions for the reference product decreased when the biosimilar came onto market. This result is expected as when cheaper "substitutes" come onto market, consumers will adjust. However for infliximab (R), the number of prescriptions of the reference biologic actually increased once the biosimilar came onto the market. However, this result could be driven by the confidential nature of the data (rather than actual utilization), as all counts below 10 are automatically censored to 0. To address this concern, I took the average of the potential numbers below 10 and changed the utilization figure to 5 in each case. In addition, there were only two months of data in which the biosimilar was

[3] When I control for FDA biosimilar approval, the magnitudes of the coefficients are slightly different; however, the direction of the estimates are the same.

prescribed once the patent expired and the utilization count for the drugs is relatively low compared to those of the other reference biologics (median ~14 prescriptions/month). These results also provide evidence showing that significant biosimilar adoption begins after observable time lags. Based on the coefficients of the time lags (significant at the 1% level), this drop occurs at ~18 months, ~24 months, and ~6 months, for filgrastim (R), somatropin (R), and insulin glargine (R) respectively. These times are verified by figures B-D[4].

For robustness checks, the results of regression **(2)** with yearly fixed effects are presented in Table A in the Appendix. Tables 4 and 5 are reported without yearly fixed effects because when they are included, the coefficient on the dummy variable indicating if a biosimilar is on the market turns from negative to positive for filgrastim (R) and insulin glargine (R). Because filgrastim (R) and insulin glargine (R) were only introduced in recent years (around 2016 and 2017), the yearly fixed effects are potentially soaking up the effect of their introduction since these products have been on the market for so few years. There may also be over identification because my year FE are highly correlated with my biosimilar available dummy for these drugs. I report the magnitudes of the FE for years 2016-2018, which are largely negative. In addition for insulin glargine (R), the coefficient on the year FE turns from positive to negative the year it enters the market, which further corroborates this story. Meanwhile, the coefficient remains negative for somatropin (R), even with yearly fixed effects – potentially because this product was on the market for much longer.

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[4] Filgrastim (R) utilization seems to be declining over time, potentially due to a related treatment being used instead. However, the only discrete and large change in quantity occurs around the time of biosimilar entrance. In addition, the total market size (utilization of reference biologic + biosimilar) seems to be leveling out around 2016-2018 when the biosimilar enters.

In order to compare the magnitude of the change in utilization across the four drug classes, Table 5 demonstrates the percent change of prescriptions instead of the number of claims. These results again highlight how biosimilar entry results in a lower utilization of three of the reference biologics, with the range being a ~60-70% decrease in the amount of prescriptions per month for the reference biologic. Again, of the drugs, infliximab (R) has an increase in utilization when the biosimilar enters; however, this is most likely due to the limited and censored data. It is also interesting to note that of the four drug classes, the biosimilar that that had the greatest impact on utilization of the reference biologic is insulin glargine (S). This was one of the biosimilars that entered the US market through the 505(b)2 pathway and the number of prescriptions per month are about 100x greater in magnitude than the other three drugs. Meanwhile, filgrastim (S) had the smallest impact on utilization, and it was the only one of the three biosimilars with negative coefficients that was approved through the BPCIA (the new act passed by Congress in 2010 to facilitate and encourage the adoption and approval of biosimilars). Thus, perhaps the magnitude of the effect of biosimilar entrance is positively correlated to the market size, and the pathway in which the drugs are approved is an important factor in determining changes in utilization.

Table 6 shows the overall monthly market share decline of the reference biologic, while Tables 7 and 8 indicate the market share decline of the reference biologic and the penetration of the individual biosimilars in the US market. Again, Table 7 shows that three of the four drugs have a significant negative coefficient on the variable indicating the number of months the drug has been on the market, while the fourth, infliximab (R) is negative, but not significant. Table 8 shows that of these three biosimilars, insulin

glargine (S) and filgrastim (S) seem to be having a greater penetration with an approximately 5.7% and 2.7% increase in market share per *month* since their entrance to the market. Compared to analysis in Europe that demonstrated that the market penetration rate for filgrastim products was 4% per *year*, this estimate seems quite large (Scott Morton et al., 2018). Because both of these products have recently entered the market compared to somatropin (S), this magnitude could be due to the fact that the US had time to learn from the European biosimilar market over the past decade, and did not have to be as concerned about safety, efficacy, and science of these new biosimilar drugs. Meanwhile somatropin (S) has been on the market since 2007, which is around the same time biosimilars started entering the market in Europe. Somatropin (S) has penetrated the market at approximately 0.38% per month, which is relatively close to the yearly penetration rate in Europe of 2.6% (Scott Morton et al., 2018). This sample of the three drugs indicates that perhaps the US has an advantage over Europe when biosimilars first enter the market, as it has time to observe adoption of these new drugs in Europe. Thus, an even greater adoption of biosimilars may be feasible if these drugs had the ability to enter the market unthreatened, instead of being tied up in frequent patent litigation.

Table 9 shows overall market share decline of the reference biologic when the biosimilar enters the market, while Table 10 shows market share decline of the reference biologic when the biosimilar enters the market separated by each drug class. Based on column 2 in Table 9, the market share decline of the reference biologic is approximately 36% when the biosimilar is available. This number is much smaller than that of the generic market, which predicts that the name brand drug only has 12% market share after one year of generic competition (Grabowski et al., 2016). Using this estimate of a 36%

decrease in market share when a biosimilar enters, I calculate future savings due to biosimilars. Assuming a prices savings of 25% (average list price savings for biosimilars tend to be 15-35%), using data about annual US sales of reference biologics from companies' annual reports, and using predicted patent expiration dates, I estimate that over the next ten years, biosimilar entry may result in savings of over $29.6 billion for the US, with a range of $14 billion to $49.2 billion (detailed description of calculations is included in the Appendix). However, if competition and pricing were to be as fierce as what has historically been seen in the generic markets (88% market share capture and 80% price savings), then savings could reach upward of $229 billion over the next ten years. (These calculations only include reference biologics that are likely to have biosimilar entry based on experience in Europe and literature review.)

7. Discussion

Although these results are largely correlational, my findings may be quite close to causal estimates, as there are few logical and reasonable explanations for the large drops in utilization of the reference biologics that occur shortly after the time when biosimilars enter the market. A potential reason that could have caused the drop in utilization for the reference biologic is new scientific knowledge that revealed detrimental side effects of the treatment around the time the biosimilar entered the market, but a detailed review of the literature did not suggest any evidence for this. Other factors that could have caused the decline in reference product utilization could be changing patient populations or other treatments that came onto the market at the same time that also treats the same disease. Although these explanations could account for the results observed here, these stories

seem unlikely and inconsistent with medical news over the period of observation: to my knowledge, none of these factors have been relevant to the drugs that this thesis studies.

Due to the small number and volume of biosimilars sold on the US market and limitations of the data, there are potential threats to external validity, as my results are notably heterogeneous across each drug class (this has also been true in other studies of early biosimilar entry – e.g. as found in Scott Morton et al., 2018). Therefore, my estimates might not be directly applicable to future biosimilars that enter the US market. In addition, biologics treat a wide variety of diseases with different patient populations so comparing them to each other may be problematic. However, the penetration of both filgrastim (S) and insulin glargine (S) are of similar magnitude and both products came to market approximately 10 years after the first biosimilar entered in Europe. Thus, perhaps the difference in the estimates for somatropin (S) is due to the uncertainty surrounding entry and competition in a brand new market, and trends are now beginning to stabilize.

My results indicate the associated quantity changes of the reference biologic when the biosimilar enters the market, and also illustrate how quickly the biosimilar is adopted. As expected, when a less expensive alternative comes to market, the quantity of the more expensive reference biologic dramatically falls, which is evidenced for each drug class in Figures B-E (and Appendix Figures A1-A3) and in Tables 2-5. (Figures F and G display all biosimilars or all reference biologics on the same graph). While the estimates of the extent of penetration for two of the biosimilars (filgrastim (S) and insulin glargine (S)) are larger than what is seen in Europe (4% per year), they are much smaller than estimates in the traditional generic market (88% per year for the first year) (Scott Morton et al., 2018; Grabowski et al., 2016). This is consistent with a story where the US

biosimilar market is learning from the European biosimilar market and some of the parties paying for medicines (primarily insurers) have seen the positive ramifications of biosimilar adoption abroad, which makes penetration of certain products faster in the US biosimilar market. However, there are still some key differences and policies between biosimilars and generics that may be preventing biosimilars from taking off as quickly as generics.

A difference between biologics and chemically synthesized drugs that is conceivably responsible for the slow uptake of biosimilars (i.e relative to traditional generics) is that biosimilars are not identical replicates of biologic drugs. Many reference product manufacturers are using this fact to undermine "the safety and effectiveness of unbranded biologic drugs" through marketing campaigns (Rowland, 2019). These campaigns have even equated biosimilars to thalidomide, a drug used to treat morning sickness in the 1950s that resulted in the babies being born with severe physical deformities (Silverman, 2002). In addition, many patients and physicians question whether those already using the reference biologic should switch to the biosimilar when it comes onto market, as it may disrupt care (Rowland, 2019). The FDA also furthers this confusion, as it has several classifications of biosimilars: those that are approved biosimilars and others that are interchangeable products (Ramakrishnan & Ching, 2018). Despite strong competition in the market for generics, we may also see less competition in the market for biosimilars because the fixed costs required for market entry are much larger for biosimilars compared to generics. Beyond these reasons, uncertainty surrounding biosimilars and biologics may lead to slower adoption and uptake of biosimilars compared to those of the generic market.

Biosimilar adoption in the US may also be influenced by insurance providers, as they control the drugs patients may get through their drug formularies, or list of drugs covered by the insurance provider. For example, insurers may be incentivized by name-brand biologic companies to keep biosimilars off their drug formularies through large rebates for the reference biologics (Sarpatwari et al., 2018). In addition to rebate traps, pharmaceutical companies may also "bundle" biologics with prices of other popular drugs, making it difficult for insurance companies to switch to cheaper biosimilars (Tribble, 2018). This tactic seems logical for reference product manufactures, as the gains from bundling are higher when the bundle contains both popular and less demanded products. Perhaps the reason for these tactics is that biologics are much more expensive and in some cases have a larger market than those of conventional chemically synthesized compounds. Because the reference biologic and its biosimilar should be considered substitutes and cheaper biosimilars should result in cost savings for insurers, reference product manufacturers may be incentivized to use non-competitive business tactics like the ones described above to prevent faster biosimilar adoption and therby extend their own profits from reference biologics. This is reflected in my analysis of utilization of biosimilars in private insurance claims.

The analysis in this thesis is limited because the dataset only covers private insurers, and I do not have data on the reimbursed prices of the reference biologic or biosimilar, individual claims, and utilization data on reference biologics that do not have biosimilars. Although analysis on pricing is out of the scope of this thesis, examining how prices change in response to biosimilar entry would be useful in understanding how the market functions and predicting future savings. However, this may be difficult

because the prices actually paid by insurers, hospitals, patients, and others are often different from the list price due to rebates and other hidden deals held secret by pharmaceutical companies, insurers, pharmacy benefit managers, etc. In addition, future research with access to individual claims data could analyze the predictive effect of patient and/or treating physician characteristics on the probability that someone receives a biosimilar. For example, are those with a lower income, certain race, or type of insurance more likely to receive a biosimilar? Or are certain types of physicians more likely to prescribe biosimilars when available? If there are observable differences across different types of users or prescribers, targeted policies can be designed and implemented to increase biosimilar adoption. Other research could attempt to use a differences-in-differences approach to determine the causal impact of biosimilar entry (where the control group would be a highly similar reference biologic that does not have a biosimilar). However, it may be difficult to satisfy the parallel trends assumption and find a proper control group, because drugs often have different patient populations and other confounding factors may make it difficult to compare one biologic to another.

8. Conclusion

Pharmaceutical costs seem to be at the forefront US lawmakers' minds, as the government tries to control spiraling healthcare expenditures. Because biologic drugs are some of the most expensive and innovative, this market is likely to be a high impact place to encourage competition, which may result in lower costs and expand access. This thesis explores the relationship between biosimilar entry and subsequent changes in quantity and finds that biosimilar penetrance is larger than evidence in European markets,

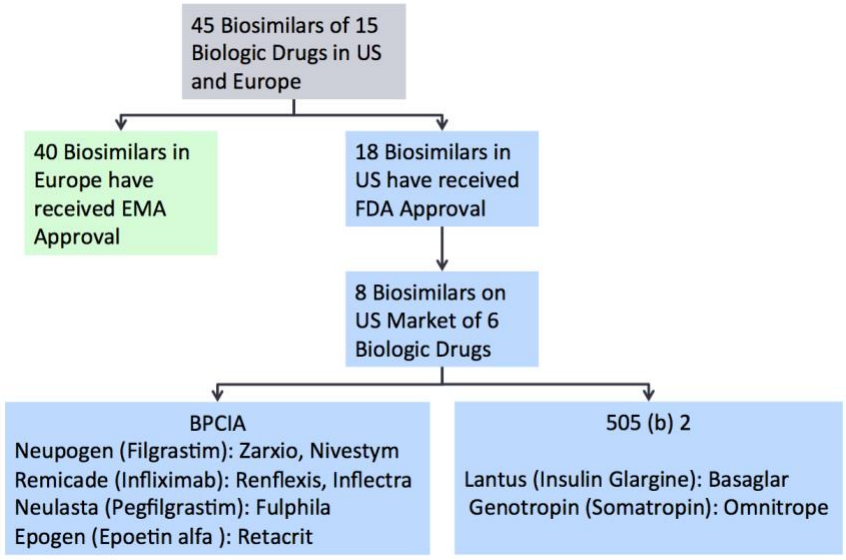
but lower than what is seen in the US generic market. I also estimate that healthcare savings over the next ten years due to biosimilar entry will be around $29 billion, with the potential to be around $229 billion if the market becomes as competitive as the US generic market. Thus, there is much work to be done so that US policy properly incentivizes biosimilar entry and adoption, which will increase competition, decrease prices, and increase access to lifesaving medicines. The US has already missed out on 10 years of potential savings that Europe had because our policies (Hatch-Waxman Act) were outdated and not applicable to innovative treatments such as biologic drugs, so it is important that our new policies are suitable for 21st century drugs.

Although this thesis illustrates that the US has had some success in adopting biosimilars, more can be done to encourage biosimilar entry that may further drive down prices. For example, policies such as the "interchangeability" status create a two-tier system in the US that does not exist in the European Medicines Agency approval process. This is potentially causing fears of safety, which pharmaceutical companies can exploit to delay take-up of biosimilars and provoke mistrust from patients and doctors. In addition, the US patent system encourages many biologics to file for non-innovative patents such as those that cover delivery mechanisms, which allows them to have an extended exclusivity period to monopolistically set prices. This further deters cheaper biosimilars from entering the market and creating competition. Thus, future reforms that target prices of biologics need to carefully consider the incentive structure surrounding polices related to biosimilar approval, safety, and efficacy. As this is still a relatively new market, more research needs to be done to understand the behavior of biosimilars because

stimulating drug price competition and wrangling in the high prices of biologics, where feasible, should be a priority.

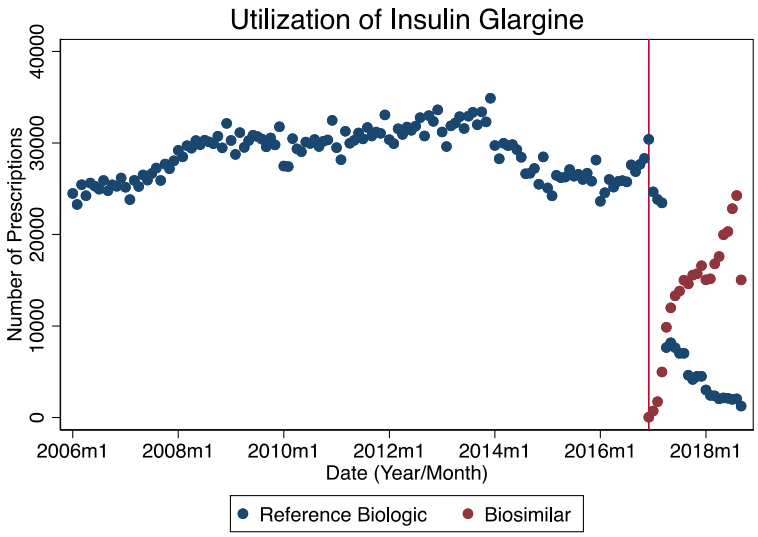
Figures

Figure A:



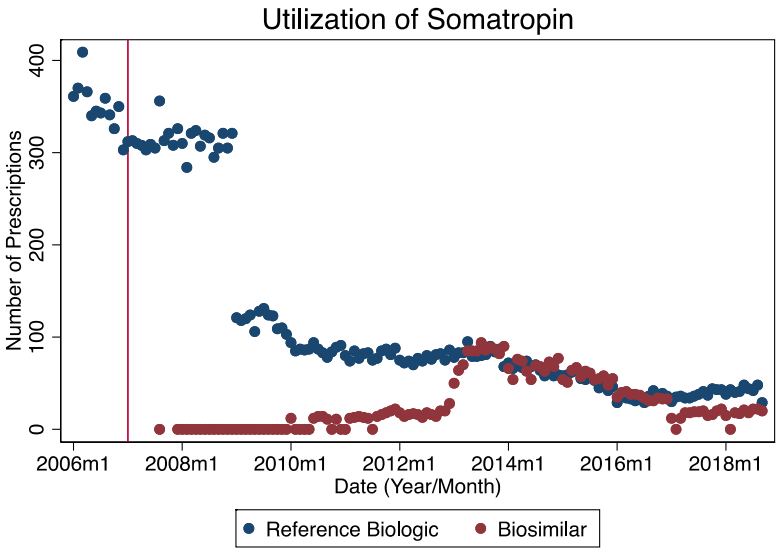
Note: Figure A provides an overall landscape of biosimilars approved in the US compared to those in Europe as of November 2018. Naming conventions in the chart are reference biologic (drug class): biosimilar(s). This thesis analyzes Neupogen, Zarxio, Remicade, Inflectra, Lantus, Basaglar, Genotropin, and Omnitrope.

Figure B



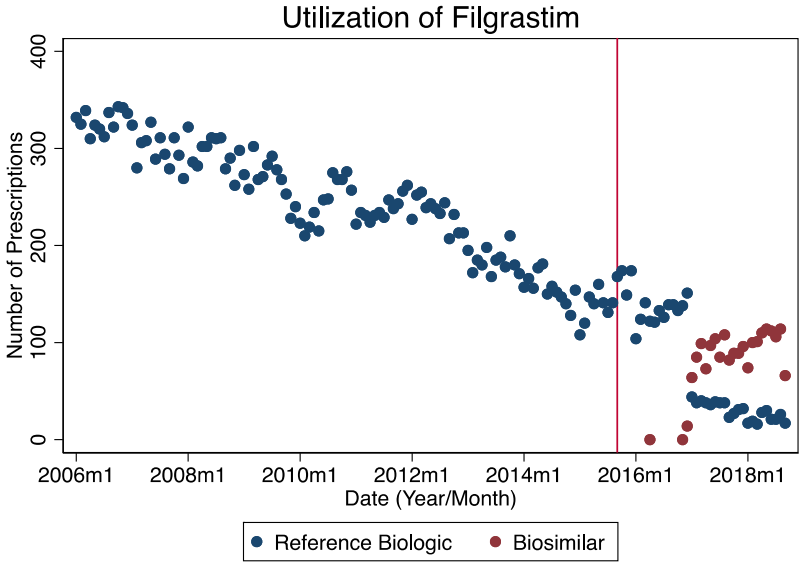
Note**:** Number of claims over time for drug class: insulin glargine (Red line indicates biosimilar market entrance/first month in which drug was available). Large drop in reference biologic occurs 5 months after biosimilar entry.

Figure C



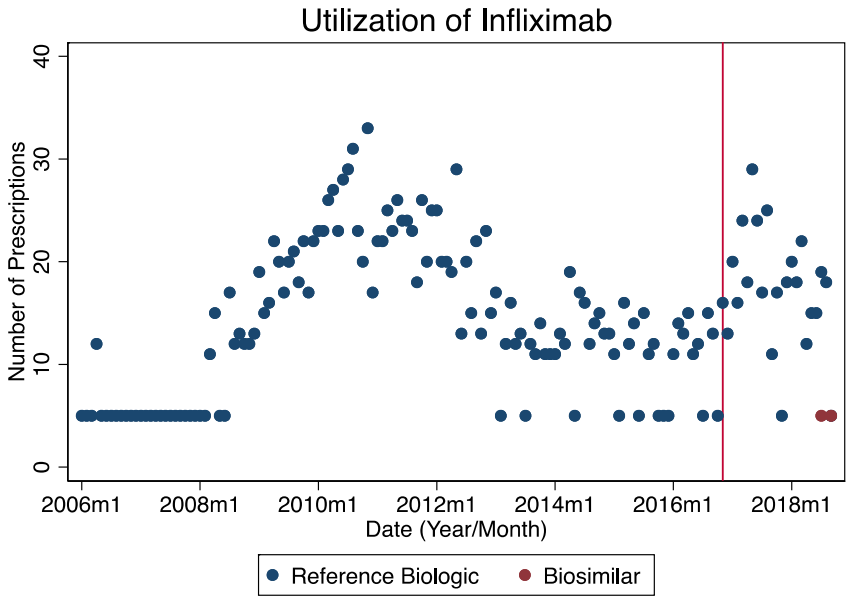
Note: Number of claims over time for drug class: somatropin. (Red line indicates biosimilar market entrance/first month in which drug was available). Large drop of reference biologic occurs at 24 months after biosimilar entry.

Figure D



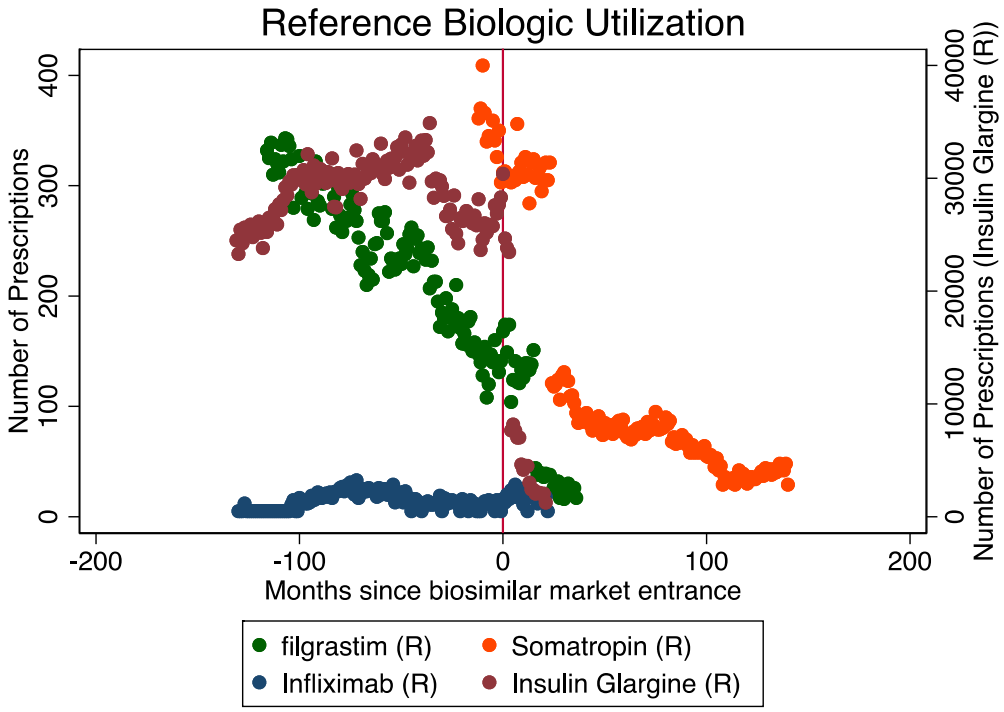
Note: Number of claims over time for drug class: filgrastim (Red line indicates biosimilar market entrance/first month in which drug was available). Large drop in reference biologic utilization occurs 17 months after biosimilar entrance.

Figure E



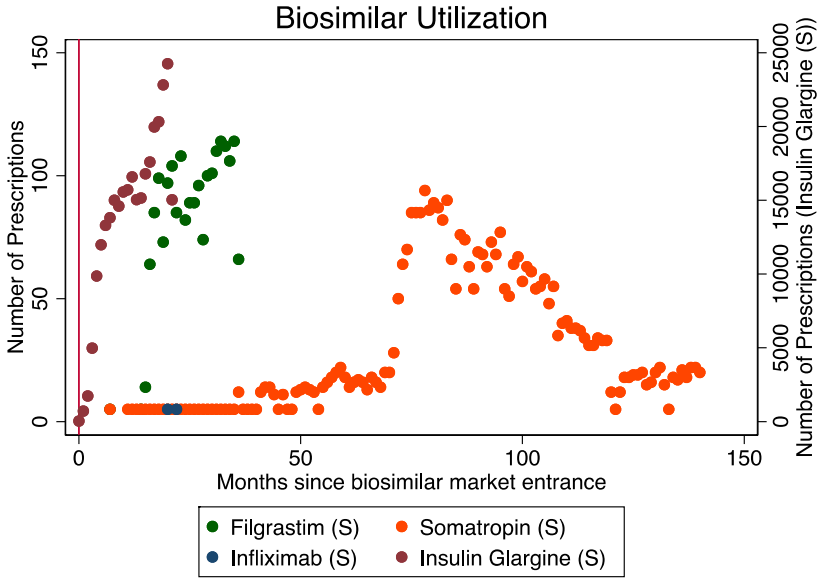
Note: Number of claims over time for drug class: Infliximab. (Red line indicates biosimilar market entrance/first month in which drug was available). Because the reference biologic utilization numbers are low, trends are less clear than the other drug classes. If utilization was below 10, then the data from Optum was censored to zero, which I changed to 5 for this analysis.

Figure F



Notes: Shows reference biologic utilization over time. The red line demonstrates the time the biosimilar in the drug class entered the market.

Figure G



Notes: Shows biosimilar utilization once it enters the market. The red line demonstrates the time the biosimilar in the drug class was first available on the market.

Tables

Table 1: List of Biosimilars approved in the US by the FDA

Drug Class	Biosimilar Name	Reference Product Name	Indications	EMA Approval (Month-Year)	FDA Approval (Month-Year)	Market Entry in US (Month-Year)
adalimumab	Cyltezo	Humira	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, ulcerative colitis, Juvenile Idiopathic Arthritis, Hidradenitis Suppurativa, Uveitis	Nov-17	Aug-17	
adalimumab	Amjevita	Humira	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, ulcerative colitis, Juvenile Idiopathic Arthritis, Hidradenitis Suppurativa, Uveitis	Mar-17	Sep-16	
adalimumab	Hyrimoz	Humira	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, ulcerative colitis, Juvenile Idiopathic Arthritis, Hidradenitis Suppurativa, Uveitis	Jul-18	Oct-18	
bevacizumab	Mvasi	Avastin	colorectal, lung, glioblastoma, kidney, cervical, and ovarian cancer.	Jan-18	Sep-17	
epoetin alfa	Retacrit	Epogen	Anemia; Cancer; Kidney Failure, Chronic	Dec-07	May-18	Nov-18
etanercept	Erelzi	Enbrel	Rheumatoid arthritis, ankylosing spondylitis, Juvenile Idiopathic Arthritis	Jun-17	Aug-16	
filgrastim	Nivestym	Neupogen	Cancer; Hematopoietic Stem Cell Transplantation; Neutropenia	Jun-10	Jul-18	Oct-18
filgrastim	Zarxio	Neupogen	Cancer; Hematopoietic Stem Cell Transplantation; Neutropenia	Feb-09	Mar-15	Sep-15
infliximab	Ixifi	Remicade	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, and ulcerative colitis		Dec-17	
Infliximab	Renflexis	Remicade	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, and	May-16	May-17	Jul-17

			ulcerative colitis			
Infliximab	Inflectra	Remicade	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, and ulcerative colitis	Sep-13	Apr-16	Nov-16
insulin glargine	Basglar *	Lantus	Type I and Type II Diabetes	Sep-14	Aug-14	Dec-16
insulin glargine	Lusduna*	Lantus	Type I and Type II Diabetes	Apr-17	Jul-17	
Pegfilgrastim	Fulphila	Neulasta	Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies		Jun-18	Jul-18
Pegfilgrastim	Udenyca	Neulasta	Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies		Nov-18	
Somatropin	Omnitrope*	Genotropin	growth hormone deficiency, Prader-Willi syndrome, Small for Gestational Age, Turner syndrome, Idiopathic Short Stature	Apr-06	May-06	Jan-07
Trastuzumab	Ogivri	Herceptin	breast, stomach, and esophageal cancer	Dec-18	Dec-17	
Trastuzumab	Herzuma	Herceptin	breast, stomach, and esophageal cancer	Feb-18	Dec-18	
Rituximab	Truxima	Rituxan	Non–Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia, Rheumatoid Arthritis, Granulomatosis With Polyangiitis (GPA) And Microscopic Polyangiitis, and Pemphigus Vulgaris	Feb-17	Nov-18	

* Indicates approval via 505(b)2

Notes: Data from table comes from various sources collected by author. Information on FDA approval dates come from FDA.gov, data on EMA approval dates come from European Medicines Agency official website (www.ema.europa.eu), data on indications come from database searches, and various dates of market entrance come from drug company announcements.

Table 2: Overall Relationship between Number of Claims and the Entrance of Biosimilar

VARIABLES	(1) Number of Claims	(2) Number of Claims	(3) Number of Claims	(4) Number of Claims
Biosimilar Available (Dummy)	-8,914.368***	-5,142***	-10,224***	-3,336***
	(733.720)	(912.2)	(792.7)	(667.9)
Drug FE	N	Y	N	Y
Year FE	N	N	Y	Y
Constant	9,792.422***	1,446***	6,439***	-311.9
	(692.902)	(252.7)	(1,572)	(230.2)
Observations	612	612	612	612
R-squared	0.130	0.900	0.143	0.909

Notes: Number of claims is number of pharmacy claims per month for the reference biologic from 2006-2018, and biosimilar available dummy is equal to 1 if there is a biosimilar on the market.
Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 3: Overall Relationship between Log(Number of Claims) and the Entrance and Approval of Biosimilar

VARIABLES	(1) Log(Number of Claims)	(2) Log(Number of Claims)	(3) Log(Number of Claims)	(4) Log(Number of Claims)
Biosimilar Available (Dummy)	-0.651***	-0.464***	-0.648***	-0.163***
	(0.085)	(0.0450)	(0.0878)	(0.0457)
Drug FE	N	Y	N	Y
Year FE	N	N	Y	Y
Constant	2.646***	2.331***	2.548***	2.338***
	(0.071)	(0.0167)	(0.190)	(0.0449)
Observations	612	612	612	612
R-squared	0.064	0.955	0.069	0.964

Notes: Log number of claims is log(number of pharmacy claims per month) for the reference biologic from 2006-2018, and biosimilar available dummy is equal to 1 if there is a biosimilar on the market.
Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 4: The Relationship between Number of Claims and the Entrance of Biosimilar by Drug Class

VARIABLES	Filgrastim (R) Number of Claims	Filgrastim (R) Number of Claims	Somatropin (R) Number of Claims	Somatropin (R) Number of Claims	Insulin Glargine (R) Number of Claims	Insulin Glargine (R) Number of Claims	Infliximab (R) Number of Claims	Infliximab (R) Number of Claims
Biosimilar Available (Dummy)	-164.674***	-93.00***	-240.9***	-41.92***	-20,772***	-9,124**	3.222**	3.795**
	(10.912)	(12.49)	(10.80)	(7.420)	(1,862)	(3,596)	(1.349)	(1.588)
Lag 6 months		-18.50		12.33*		-13,869***		2.667
		(11.57)		(7.215)		(3,636)		(2.897)
Lag 12 months		-23.17		-10.67		-3,074***		-4.667
		(19.90)		(9.024)		(684.3)		(3.458)
Lag 18 months		-69***		-0.333		-902.7**		-1.433
		(19.64)		(6.866)		(391.5)		(3.278)
Lag 24 months		-14.47***		-241.9***				
		(1.616)		(4.666)				
Constant	241.836***	241.8***	351.1***	351.1***	28,818***	28,818***	14.04***	14.04***
	(5.645)	(5.721)	(7.199)	(7.296)	(232.3)	(234.7)	(0.649)	(0.656)
Observations	153	153	153	153	153	153	153	153
R-squared	0.584	0.661	0.334	0.954	0.762	0.871	0.025	0.040

Notes: Number of claims is number of pharmacy claims per month for the reference biologic from 2006-2018, and biosimilar available dummy is equal to 1 if there is a biosimilar on the market. Lags are for the biosimilar available dummy.

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 5: The Relationship between Log(Number of Claims) and the Entrance and Approval of Biosimilar by Drug Class

VARIABLES	Filgrastim (R) Log(Number of Claims)	Filgrastim (R) Log(Number of Claims)	Somatropin (R) Log(Number of Claims)	Somatropin (R) Log(Number of Claims)	Insulin Glargine (R) Log(Number of Claims)	Insulin Glargine (R) Log(Number of Claims)	Infliximab (R) Log(Number of Claims)	Infliximab (R) Log(Number of Claims)
Biosimilar Available (Dummy)	-0.620***	-0.203***	-0.623***	-0.0542***	-0.753***	-0.221**	0.129***	0.167***
	(0.061)	(0.0367)	(0.0273)	(0.00916)	(0.0860)	(0.101)	(0.0452)	(0.0419)
Lag 6 months		-0.0507		0.0164*		-0.484***		0.0474
		(0.0366)		(0.00951)		(0.110)		(0.0679)
Lag 12 months		-0.146		-0.0145		-0.330***		-0.135
		(0.106)		(0.0123)		(0.0658)		(0.108)
Lag 18 months		-0.387***		-0.000257		-0.165**		-0.0383
		(0.106)		(0.00977)		(0.0673)		(0.133)
Lag 24 months		-0.219***		-0.688***				
		(0.0294)		(0.0173)				
Constant	2.368***	2.368***	2.544***	2.544***	4.458***	4.458***	1.076***	1.076***
	(0.011)	(0.0113)	(0.00884)	(0.00896)	(0.00354)	(0.00358)	(0.0232)	(0.0234)
Observations	153	153	153	153	153	153	153	153
R-squared	0.626	0.871	0.248	0.797	0.741	0.948	0.032	0.043

Notes: Log number of claims is log(number of pharmacy claims per month) for the reference biologic from 2006-2018, and biosimilar available dummy is equal to 1 if there is a biosimilar on the market. Lags are for the biosimilar available dummy.

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 6: Overall Market Share Decline of Reference Biologics Overtime

VARIABLES	(1) Market Share	(2) Market Share	(3) Market Share	(4) Market Share
Months since biosimilar entrance	-0.004***	-0.00532***	-0.00267***	-0.00253***
	(0.000)	(0.000388)	(0.000195)	(0.000463)
Drug FE	N	Y	N	Y
Year FE	N	N	Y	Y
Constant	0.958***	0.918***	1***	0.970***
	(0.007)	(0.0169)	(0.0224)	(0.0119)
Observations	612	612	612	612
R-squared	0.339	0.405	0.548	0.575

Notes: Months since biosimilar entrance is the number of months since the biosimilar entered the market. Market share is for reference biologics from 2006-2018.

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 7: Market Share decline of Reference Biologic by Drug Class

VARIABLES	Filgrastim (R) Market Share	Somatropin (R) Market Share	Insulin Glargine (R) Market Share	Infliximab (R) Market Share
Months since biosimilar entrance	-0.027***	-0.00382***	-0.0567***	-0.00414
	(0.001)	(0.000242)	(0.00300)	(0.00275)
Constant	1.010***	1.010***	0.990***	1.002***
	(0.004)	(0.0100)	(0.00334)	(0.00153)
Observations	153	153	153	153
R-squared	0.894	0.644	0.929	0.200

Notes: Months since biosimilar entrance is the number of months since the biosimilar entered the market. Each column contains data from 2006-2018 for a different reference biologic

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 8: Penetration of Biosimilar by Drug Class

VARIABLES	Filgrastim (S) Market Share	Somatropin (S) Market Share	Insulin Glargine (S) Market Share	Infliximab (S) Market Share
Months since biosimilar entrance	0.027***	0.00382***	0.0567***	0.00414
	(0.001)	(0.000242)	(0.00300)	(0.00275)
Constant	-0.010**	-0.0103	0.00962***	-0.00222
	(0.004)	(0.0100)	(0.00334)	(0.00153)
Observations	153	153	153	153
R-squared	0.894	0.644	0.929	0.200

Notes: Months since biosimilar entrance is the number of months since the biosimilar entered the market. Each column contains data from 2006-2018 for a different biosimilar.

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Table 9: Overall Relationship between Biosimilar Entry and Market Share Decline of Reference Biologic

VARIABLES	(1) Market Share	(2) Market Share	(3) Market Share	(4) Market Share
Biosimilar Available (Dummy)	-0.303***	-0.363***	-0.212***	-0.175***
	(0.019)	(0.0349)	(0.0151)	(0.0340)
Drug FE	N	Y	N	Y
Year FE	N	N	Y	Y
Constant	1.000	0.982***	1.000	0.983***
	(0.000)	(0.0117)	(0.000)	(0.0130)
Observations	612	612	612	612
R-squared	0.409	0.453	0.541	0.567

Notes: Market share is the reference product market share per month for the reference biologic from 2006-2018, and biosimilar available dummy is equal to 1 if there is a biosimilar on the market.

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Table 10: Relationship between Biosimilar Entry and Market Share Decline of Reference Biologic by Drug Class

VARIABLES	Filgrastim (R) Market Share	Somatropin (R) Market Share	Insulin Glargine (R) Market Share	Infliximab (R) Market Share
Biosimilar Available (Dummy)	-0.436***	-0.256***	-0.662***	-0.0308
	(0.062)	(0.0172)	(0.0645)	(0.0228)
Constant	1.000	1.000	1.000	1***
	(0.000)	(0.000)	(0.000)	(0)
Observations	153	153	153	153
R-squared	0.505	0.111	0.806	0.064

Notes: Market share is the reference product market share per month for the reference biologic from 2006-2018, and biosimilar available dummy is equal to 1 if there is a biosimilar on the market. Each column contains data from 2006-2018 for a different reference biologic.

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Appendix

Table A: The Relationship between Number of Claims and the Entrance of Biosimilar by Drug Class with Fixed Effects

VARIABLES	Filgrastim (R) Number of Claims	Somatropin (R) Number of Claims	Insulin Glargine (R) Number of Claims	Infliximab (R) Number of Claims
Biosimilar Available (Dummy)	22.917***	-296.9***	4,280***	5.071*
	(6.594)	(6.219)	(425.2)	(2.677)
Biosimilar Approved (Dummy)	29.333***	-38.13***	-2,412***	-3.238
	(5.856)	(11.61)	(521.4)	(2.549)
…				
YEAR = 2016	-249.833***	-6.778***	3,456***	11.67***
	(8.531)	(2.195)	(711.0)	(1.261)
YEAR = 2017	-345.417***	-3.861*	-16,338***	15.42***
	(7.933)	(2.274)	(2,488)	(2.765)
YEAR = 2018	-359.083***		-24,784***	12.61***
	(7.927)		(727.4)	(2.738)
Constant	328.500***	376.5***	25,072***	1
	(3.289)	(9.984)	(229.8)	(1.008)
Observations	153	153	153	153
R-squared	0.976	0.994	0.917	0.713

Notes: Around 2016, filgrastim (S) entered the market, which is evidenced by the large and negative coefficient on the year dummy 2016. Meanwhile around 2017, insulin glargine (S) entered the market, which is why the year FE switched from positive to negative. Both indicate that these year FE are potentially absorbing the effect of the biosimilar available dummy since the biosimilar was on the market for so few years.

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table B: Selected Regressions with Control for Biosimilar Approval for Reference Biologic

VARIABLES	(1) Number of Claims	(2) Number of Claims	(3) Log(Number of Claims)	(4) Log(Number of Claims)	(5) Market Share
Biosimilar Available (Dummy)	-3,991***	-2,563***	-0.442***	-0.298***	-0.367***
	(971.835)	(637.0)	(0.0444)	(0.0428)	(0.0328)
Drug FE	Y	Y	Y	Y	Y
Year FE	N	Y	N	Y	N
Controls	Y	Y	Y	Y	Y
Constant	1,561.487***	-212.5	2.333***	2.320***	0.982***
	(254.024)	(218.5)	(0.0166)	(0.0445)	(0.0114)
Observations	612	612	612	612	612
R-squared	0.901	0.910	0.955	0.965	0.453

Notes: Control is a biosimilar approved dummy that is equal to 1 if it has FDA approval that month. Data on Number of Claims, Log Number of Claims, and Market Share is monthly from 2006-2018 for Reference Biologics.

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table C: Selected Regressions with Control for Biosimilar Approval by Drug Class

VARIABLES	Filgrastim (R) Log(Number of Claims)	Somatropin (R) Log(Number of Claims)	Insulin Glargine (R) Log(Number of Claims)	Infliximab (R) Log(Number of Claims)
Biosimilar Available (Dummy)	-0.407***	-0.608***	-0.715***	0.207**
	(0.061)	(0.0269)	(0.0862)	(0.0837)
Controls	Y	Y	Y	Y
Constant	2.380***	2.575***	4.468***	1.081***
	(0.011)	(0.0108)	(0.00381)	(0.0242)
Observations	153	153	153	153
R-squared	0.642	0.248	0.745	0.037

Notes: Control is a biosimilar approved dummy that is equal to 1 if it has FDA approval that month. Data on Log Number of Claims is monthly from 2006-2018 for reference biologic separated by drug class.

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Estimates of Savings

Estimated savings=annual sales • years of saving • market share capture•25% (for the price discount)
Total= Sum of estimated savings for all reference biologics

Reference Biologic	Annual US sales 2017 or year before biosimilar entrance (Million USD)	Projected Patent Expiration	Years of Savings	Biosimilar Market Share Capture	Estimated Savings (Millions USD)
Humira	12,361	2023	6	0.363	6730.5645
Avastin	2987	2019	10	0.363	2710.7025
Enbrel	5,206	2028	1	0.363	472.4445
Rituxan	4137	2018	10	0.363	3754.3275
Herceptin	2700	2019	10	0.363	2450.25
Neupogen	1,159	Already Expired	10	0.363	1051.7925
Lantus	3,900	Already Expired	10	0.363	3539.25
Genotropin	232	Already Expired	10	0.363	210.54
Remicade	4525	Already Expired	10	0.363	4106.4375
Epogen	1096	Already Expired	10	0.363	994.62
Neulasta	3931	Already Expired	10	0.363	3567.3824
Total					29588.3115

Conservative Estimate

Estimated savings=annual sales • years of saving • market share capture (lower bound of CI in Table 9 Column 2) •15% (for the price discount)

Total= Sum of estimated savings for all reference biologics

Reference Biologic	Annual US sales 2017 or year before biosimilar entrance (Million USD)	Projected Patent Expiration	Years of Savings	Biosimilar Market Share Capture	Estimated Savings (Millions USD)
Humira	12,361	2023	6	0.295	3281.8455
Avastin	2987	2019	10	0.295	1321.7475
Enbrel	5,206	2028	1	0.295	230.3655
Rituxan	4137	2018	10	0.295	1830.6225
Herceptin	2700	2019	10	0.295	1194.75
Neupogen	1,159	Already Expired	10	0.295	512.8575
Lantus	3,900	Already Expired	10	0.295	1725.75
Genotropin	232	Already Expired	10	0.295	102.66
Remicade	4525	Already Expired	10	0.295	2002.3125
Epogen	1096	Already Expired	10	0.295	484.98
Neulasta	3931	Already Expired	10	0.295	1739.4675
Total					14427.3585

High Estimate

Estimated savings=annual sales • years of saving • market share capture (upper bound of CI in Table 9 Column 2) •35% (for the price discount)
Total= Sum of estimated savings for all reference biologics

Reference Biologic	Annual US sales 2017 or year before biosimilar entrance (Million USD)	Projected Patent Expiration	Years of Savings	Biosimilar Market Share Capture	Estimated Savings (Millions USD)
Humira	12,361	2023	6	0.4315	11200.92015
Avastin	2987	2019	10	0.4315	4511.11675
Enbrel	5,206	2028	1	0.4315	786.23615
Rituxan	4137	2018	10	0.4315	6247.90425
Herceptin	2700	2019	10	0.4315	4077.675
Neupogen	1,159	Already Expired	10	0.4315	1750.37975
Lantus	3,900	Already Expired	10	0.4315	5889.975
Genotropin	232	Already Expired	10	0.4315	350.378
Remicade	4525	Already Expired	10	0.4315	6833.88125
Epogen	1096	Already Expired	10	0.4315	1655.234
Neulasta	3931	Already Expired	10	0.4315	5936.79275
Total					49240.49305

Notes: Data on annual US sales comes from financial annual reports from reference product manufacturers and information on projected patent expiration dates comes from various sources collected by author.

Figure A.1

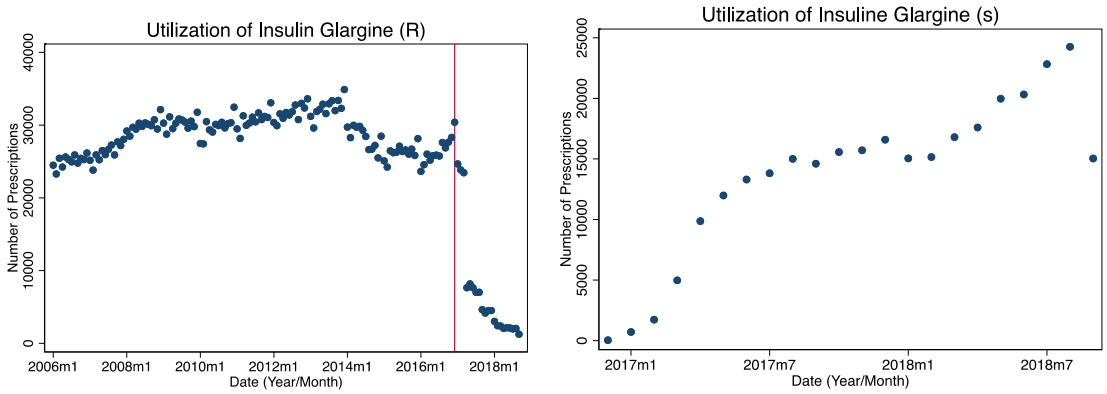


Figure A.2

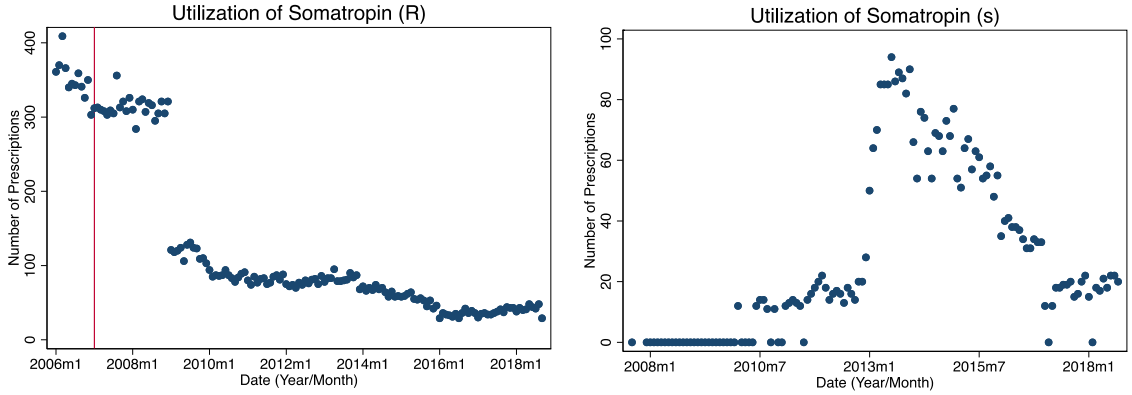
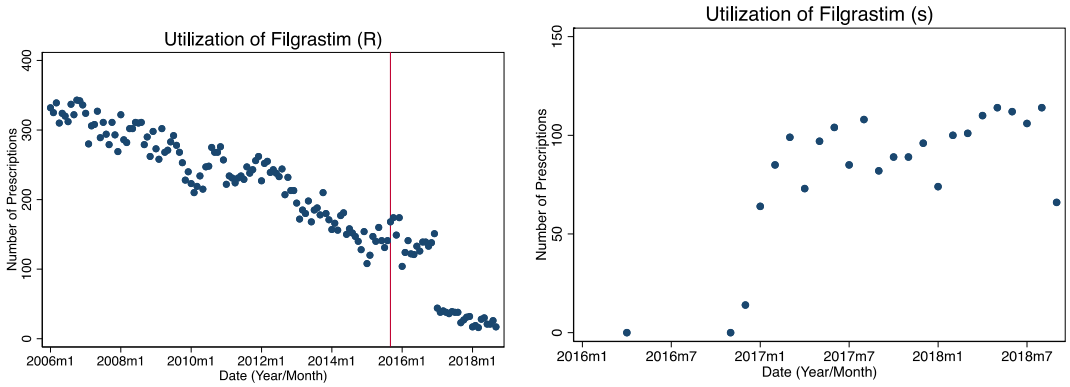


Figure A.3



Notes: Figures A.1-A.3 separate the information shown in figures B-E. Reference biologic is separated from biosimilar.

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