Biosimilar Entry and the Pricing of Biologic Drugs*

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Abstract

Unlike small-molecule drugs, biologics cannot be exactly replicated, and instead face post-exclusivity competition from inexact copies known as biosimilars. Under a stylized model, greater perceived differences between incumbent and entrant can cause incumbents to "fight" rather than "acquiesce." Consistent with this prediction, we find that, in the U.S. market, biologics respond to biosimilar entry by reducing net-of-rebate prices to maintain volume, in contrast to the well-documented response of small-molecule drugs to generic entry. We exploit variation in biosimilar entry mechanisms created by the 2009 Biologics Price and Competition Act to provide further suggestive evidence that perceived differences drive the observed outcomes.

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Pharmaceutical market regulation grants temporary monopoly power to new drugs. Once this protection expires, identical generic competitors quickly enter the market at much lower prices, typically capturing all but a small share of the market previously held by the original brand drug. The economic rationale behind the regulation is well known: society trades off the temporary inefficiency of monopoly power in order to incentivize the development of valuable innovation. The natural life-cycle of pharmaceutical products, however, breaks down in the case of biologic drugs: those comprised of large molecules grown from organic tissue (unlike more traditional, chemically synthesized small-molecule drugs). The production process of biologic drugs is so complex that it is impossible for anyone other than the original manufacturer to replicate the drug exactly. This prevents potential entrants from exploiting the low-cost abbreviated approval mechanisms available to copiers of small-molecule drugs, often resulting in biologic manufacturers maintaining monopoly power indefinitely.

The United States Congress attempted to address this issue by passing the Biologics Price And Competition Act (BPCIA) in 2009. The BPCIA created an abbreviated approval pathway for so-called *biosimilar* products: copies of a reference biologic that are highly similar in terms of structure, biological activity, efficacy, and safety. One of the goals of the BPCIA was to create greater competition and lower prices in markets where generics cannot enter.[1] However, while generics can claim to be exact copies of their reference product, biosimilars cannot. As a result, passage of the Act was accompanied by significant doubts about the ability of biosimilars to capture market share and reduce overall spending. A large factor contributing to this uncertainty concerned the response of reference biologics: would they "acquiesce" to the entry of biosimilars, like innovator brands do with generic products, or would they try to compete with biosimilars on price?

In this article, we study the reaction of reference biologics to the approval and en-

[1]See written remarks by Janet Woodcock and Peter Marks at https://www.fda.gov/news-events/fda-voices/ensuring-innovation-and-competition-biologics-leads-more-timely-products-patients, retrieved December 2020.

try of biosimilar products in the United States, and compare it to that of brand products to generic competition. To model competition with a "copycat" competitor, we use a version of the seminal model of brand and generic competition by Frank and Salkever (1992). In the model, an incumbent sets a single price to serve both a "loyal" and a "price-sensitive" segment of the market, and faces competition from a same-molecule entrant in the price-sensitive segment only. We model competition in this latter segment using a Hotelling model in which the entrant differs both because of travel costs and because it can have lower vertical quality. The key prediction of the model is that the incumbent will raise prices and focus on the loyal market if it faces competition from a copycat product of similar (vertical and horizontal) quality. This is usually how incumbents respond to the entry of generic drugs. Conversely, if the copycat entrant is perceived to be different enough, the incumbent may find it profitable to compete for customers in the price-sensitive segment by lowering price. Because biosimilars are not considered identical copies, our hypothesis is that originator biologics may adopt a more aggressive pricing strategy in response to biosimilar entry.

We empirically evaluate the predictions of the model by examining the impact of biosimilar entry on incumbent prices and insurance coverage, using a generalized difference-in-differences framework. Our treatment group consists of incumbent biologics with an actively marketed biosimilar competitor, with the broader set of biologic drugs serving as the control group. The outcomes we examine come from a rich dataset on pricing and access to biologic drugs that includes information on list prices, estimated net prices, volume sales, and formulary status.

Our results are consistent with the predictions of the model: we find that reference biologics lower prices in response to biosimilar entry, in order to maintain sales volume and formulary status. After biosimilar entry, reference biologics experience a significant fall in net price of about 20 percent, a small, noisy decline in volume sales, and a small but significant decline in formulary coverage. Although selection remains a concern, we

do not observe significant pre-trends in any of the outcomes of interest. The results are robust to alternative definitions of the control group and to allowing for more flexible specifications. Our robustness checks also address some of the concerns recently raised by the literature on difference-in-difference estimators (Callaway and SantAnna, 2020; Goodman-Bacon, 2021). The decline in net price comes almost entirely from increased discounts, as list prices are unaffected. These results suggest that manufacturers of reference biologics react to biosimilar entry by offering larger rebates to PBMs and large payers in order to maintain formulary status, and, in turn, sales volume. Overall, these efforts seem to be relatively successful, as we detect only small changes in these two variables. The response stands in stark contrast to the response of brand drugs to generic entry (see e.g., Berndt and Aitken, 2011; Grabowski and Vernon, 1992; Grabowski et al., 2016). Brand drugs rarely attempt to compete on price with generic entrants, preferring instead to maintain prices and sell to a small number of patients with strong brand preferences.

The model suggests that the contrasting responses of biologic and small molecule incumbents may be driven by greater perceived differences for biosimilars, and we provide further evidence for this mechanism by exploiting variation in the regulation of biosimilar and biologic products. As noted earlier, the BPCIA created an abbreviated pathway to approval for biosimilars in 2009. Before 2009, two biosimilars were approved through the regular approval channels as if they were completely new drugs. After 2009, two other biosimilar products that were ineligible for the BPCIA pathway were approved using a third channel.[2] We find that, in this limited subsample, reference biologics experienced a much greater drop in formulary status and experienced minimal changes in price, in contrast to biologics that faced biosimilars approved through the abbreviated pathway.

The model and empirical analysis highlight the potential role played by perceived quality in determining the pricing strategy of reference biologics. The evidence we col-

[2]The two ineligible biosimilars are insulin products, which—despite insulin being a biologic drug in nature—the FDA did not classify as biosimilars until recently. Section 3.2 provides more details on these four drugs.

lect is consistent with a widely-held perception that biosimilars have lower quality than reference biologics. While medical studies suggest a high degree of substitutability between reference biologics and their biosimilar counterparts (see e.g., Barbier et al., 2020; Luttropp et al., 2020), familiarity of biosimilars among patients and physicians remains relatively low. According to a recent HarrisX poll, 65 percent of Americans admit to not being familiar with the term "biosimilars."[3] Another survey focusing on prescribing physicians found that about 40 percent were not aware that biosimilars were as safe, or had the same efficacy as their originator counterparts (Cohen et al., 2016). Thus, disseminating information about the substitutability of biosimilars, as the recently-passed Advancing Education on Biosimilars Act aims to do, may lead to equilibrium outcomes that more closely resemble those in small-molecule markets. Even without policy interventions, we expect that as patients and providers become more familiar with biosimilars over time, incumbent biologics will no longer compete on price with biosimilars, leading to greater biosimilar penetration and lower overall spending.[4]

This article contributes to the growing literature on the impact of biosimilars by studying the competitive interactions between biologics and biosimilars. In doing so, we uncover an explanation that can potentially reconcile the contrasting views on biosimilar entry in the U.S. market. Several papers in this literature (see e.g., Atteberry et al., 2019; Trusheim et al., 2019; Zhai et al., 2019) have described the current regulation of biologics markets as an overall failure, due to the inability of biosimilars to gain meaningful market share.[5] Other studies, however, have identified some positive contributions in the form of lower prices (see e.g., Brill and Ippolito, 2019; San-Juan-Rodriguez et al., 2019). We find heterogeneous responses: while some biosimilars have been able to establish them-

[3]For poll results, see harrisx.com/wp-content/uploads/2020/03/Biosimilars-topline-poll-public-memo-VF.pdf, retrieved November 13, 2020.

[4]Pockets of the U.S. healthcare system have already managed to achieve biosimilar penetration rates on par with those of generic drugs. See, e.g., Kaiser Permanente in California: https://biosimilarsrr.com/2019/11/07/how-did-kaiser-permanente-reach-95-utilization-of-biosimilar-herceptin-and-avastin-so-quickly/, retrieved November 12, 2020.

[5]Appendix C.3 uses data from Medicare Part B to show that most biosimilars do struggle to gain market share, though there are exceptions.

selves as viable market options, others have been actively fought by reference biologics and been unable to gain market share from the originator. Our theoretical model points to perceived quality differences as a potential driver of these different outcomes. To the best of our knowledge, ours is also the first systematic study of biosimilars in the U.S. market. This literature also includes analysis of the penetration of biosimilars in European markets by Scott Morton et al. (2018). The authors focus on variation in procurement mechanisms across countries as a predictor of penetration.

More broadly, we contribute to the literature on competition in pharmaceutical markets. In particular, we join a series of recent papers showing that strategic behavior of pharmaceutical companies is rarely reflected in widely available list prices, but instead becomes apparent only through movements in net price, which are much harder—but not impossible—to track (see, e.g., Feng et al., 2020; Kakani et al., 2020). Finally, our paper is one of a small but growing number of studies that examines access in the pharmaceutical market by using formulary data (see, e.g., Geruso et al., 2019; Lavetti and Simon, 2018).

The rest of the paper proceeds as follows. Section 1 provides background on biologic and biosimilar drugs. Section 2 introduces the model of competition between an incumbent and a same-molecule entrant. Section 3 presents the data, empirical framework, and results. Section 4 concludes.

1 Characteristics and Regulation of Biologic Drugs

1.1 Background on Biologics and the BCPIA

Biopharmaceutical products, more commonly known as biologic drugs or biologics, are large, complex molecules grown from organic material. Examples of biologic drugs include insulin, interferons (used to treat multiple sclerosis, some types of cancers, and hepatitis), and monoclonal antibodies (used to treat rheumatoid arthritis, psoriasis, and ulcerative colitis).

Because of their complexity, biologics cannot be reproduced exactly. This makes them fundamentally different from more traditional, "small-molecule" drugs, which are synthesized using perfectly replicable chemical processes. Instead, biologics are grown inside living organisms that have very specific cell lines. Only the company that manufactures the original biologic drug has access to the specific cell line used in the production process. Therefore, no other company can ever create an exact copy. Nonetheless, it is still possible to create a "biosimilar" version of an existing biologic drug: one that contains the same components but may present small differences due to the complexity of the production process.[6]

The impossibility of reproducing exact copies of biologic drugs means that most existing regulations managing drug competition over the product life-cycle do not apply to biologics. For example, generic drugs have enjoyed access to an accelerated approval process since the passage of the 1984 Hatch-Waxman Act. In particular, the Abbreviated New Drug Application (ANDA) process waives the requirement to provide clinical trial data for generic products. However, biosimilar drugs cannot apply through the ANDA process, and, until recently, would have had to undergo clinical testing as completely new drugs.

The Biologics Price Competition and Innovation Act (BPCIA) of 2009 attempted to address the gaps in the regulation of biosimilars by creating an abbreviated approval pathway for these drugs. Under the BPCIA, approval of a biosimilar product has two main criteria: (i) presentation of chemical data showing that the product is highly similar to the reference biologic in structure; and (ii) evidence of equivalence with the reference biologic from a clinical trial.

Although the BPCIA makes it easier to bring biosimilars to market, they still face three significant hurdles relative to generic drugs. First, the cost of developing a biosimilar is

[6] As defined by the Food and Drug Administration (FDA), a "biosimilar" is a biologic that is highly similar to, with no clinically meaningful differences from, an existing reference or innovator biologic already in production. The phrase "meaningful differences" refers to the efficacy and safety of the biosimilars in comparison to the reference biologic.

still much higher than developing a generic. Informal estimates place the cost of bringing a biosimilar drug to market between $100 million and $250 million, which, while much lower than the cost to bring a new drug to market, far surpass the development cost of a generic small-molecule drug (about $2–$5 million) (Grabowski et al., 2014).[7] This cost difference stems from both the complicated nature of biologic drugs and the clinical trial requirement of the BPCIA. Second, biosimilars face much higher risk of litigation from the incumbent biologic manufacturer. Biologic drugs are protected by a much larger number of patents relative to small-molecule drugs, and infringement of any of these patents is enough to prevent a biosimilar from entering (Chen et al., 2017). Third, biosimilars cannot take advantage of regulation that promotes the use of generic products, such as mandatory substitution laws.

1.2 Biosimilar Approvals and Launches

Figure 1 plots the approval and launch timeline of all thirty-two biosimilars approved for use in the United States as of July 2020.[8] A dashed line in the graph represents a product that has been approved, but not launched, while a solid line represents a launched product. One noticeable pattern is the long delay between approval and launch, which often lasts multiple years. Only eighteen of these biosimilars, covering a total of ten molecules, are available for sale. Some of them, like Amjevita (a biosimilar of Humira), have not launched due to agreements with the manufacturer of the reference biologic (Barlas, 2019). Others are still tied up in litigation.[9]

Four of the products we include are effectively biosimilars but were not approved

[7] See remarks made by FDA Commissioner Scott Gottlieb to the America's Health Insurance Plans' National Health Policy Conference on March 7, 2018 (https://www.fda.gov/news-events/speeches-fda-officials/capturing-benefits-competition-patients-03072018, retrieved November 3, 2020). Estimates place the cost of developing a new drug at around $2.87 billion (DiMasi et al., 2016).

[8] Since then, two other biosimilars have been approved and launched: Semglee, an interchangeable biosimilar for Lantus, and Riabni, a biosimilar of Rituxan.

[9] This also raises the issue that the biologic manufacturer may have some control over the timing of entry. Even if this were the case, our results could still be interpreted as the impact of entry of biosimilars under current market conditions, which incorporates the potentially mitigating impact of litigation on entry.

through the accelerated pathway introduced by the BPCIA. These are Admelog (biosimilar of Humalog), Basaglar (Lantus), Extavia (Betaseron), and Granix (Neupogen). Extavia and Granix applied for marketing approval before the abbreviated pathway was introduced.[10] Admelog and Basaglar are insulin products, which the FDA did not consider to be biologics until 2020.[11] As a result, these two drugs were approved through a pathway called 505(b)(2), which is usually reserved for follow-on products of existing brands.

2 A Model of Strategic Responses to Copycat Entry

In this section, we consider a model of competition between an established brand and a copycat entrant, akin to a generic or store brand of an established product. Empirical evidence on competition between these kinds of products usually shows a persistent price differential between the two products, despite their similarity (see e.g., Bronnenberg et al., 2015; Sethuraman and Cole, 1999; Shrank et al., 2009; Steenkamp et al., 2010). Moreover, even when the price differential is very large, the brand product retains some market share.

In the context of pharmaceutical products, the seminal model that explains these empirical facts comes from Frank and Salkever (1992) (hereafter, FS). FS suggests that the observed equilibrium may be driven by the presence of a small segment of the market willing to pay a premium for the brand product. In the context of biosimilars, the presence of this "loyal" segment with inelastic preference for the originator biologic could be justified by a combination of physician incentives, lack of information, and inertia. Most biologic products are administered in an outpatient setting, and physicians (especially

[10] Extavia was approved in 2009. Granix was approved in 2012, but submitted its first application to the FDA in 2009 (see https://www.drugs.com/nda/xm02_091202.html, retrieved November 10, 2020).

[11] While insulin *is* a biologic drug, it was first marketed in the U.S. before the word "biologic" entered in the official U.S. regulation terminology. As a result, it was not considered as such. The FDA closed this loophole in February 2020, publishing a rule that included insulins among the products eligible for approval under the abbreviated BPCIA pathway (see https://www.fda.gov/news-events/press-announcements/fda-works-ensure-smooth-regulatory-transition-insulin-and-other-biological-products, retrieved November 10, 2020).

those working in hospitals that are part of the 340B program) may earn more from prescribing biologics over their biosimilar counterpart (Mulcahy et al., 2018; Smeeding et al., 2019). Moreover, a recent survey of U.S. physicians shows that most doctors are reluctant to prescribe biosimilars as long as the originator biologic is also covered by the hospital formulary (Kolbe et al., 2021). Finally, most biologics can be categorized as maintenance drugs for chronic conditions. Evidence suggests that doctors rarely switch patients to a new entrant unless the entrant is significantly higher in quality (Feng, 2020).

To describe competition between biologics and biosimilars, we adapt the FS framework by introducing explicit horizontal and vertical quality differences between the brand incumbent and the generic (or biosimilar) entrant. These quality measures are proxies for real world concerns such as whether the safety and efficacy profile of biosimilars truly matches that of their biologic counterparts.

2.1 Model Setup

The FS model speculates that the pricing strategy of brand products in response to generic entry may be driven by the presence of a small segment of the market willing to pay a premium in order to keep using the brand product. The paper models this "loyal" segment of the demand curve as having an inelastic preference for brand products.

We parametrize the FS framework to explicitly incorporate the role of perceived differences between incumbent brand and generic (or, in our case, biosimilar) entrant. Intuitively, entry from a same-molecule entrant that is perceived as very similar would generate strong competition in the market. Without a loyal consumer segment, this would result in lower incumbent prices. However, in markets with a loyal segment, the result can reverse. Stronger competition may encourage the incumbent to price only to the loyal segment to avoid competing with the entrant on price.[12]

[12]We use the term perceived difference, because, while there could be real differences between incumbents and copycat entrants, consumer behavior may also be driven by an information gap surrounding the effectiveness and safety of the entrant, as suggested by recent empirical evidence from Bronnenberg et al. (2015) on the purchasing patterns of informed and uninformed consumers.

We focus on the setup and main predictions here, and present a full derivation of the model in Appendix B. In the original setup of FS, the originator's demand function is divided in two segments, $D_L(p_b)$ and $D_S(p_b, p_g)$. The subscripts L and S respectively indicate a "loyal" segment of patients—those who will never switch to a generic alternative—and a segment that is "sensitive" to price. p_b and p_g denote the price of the (brand or biologic) incumbent product and the price of the (generic or biosimilar) entrants.

We model demand in the loyal segment as a measure α of homogeneous consumers with valuation V_b for the brand product, and 0 for the generic product. Demand in the price sensitive market based on the Hotelling model. A measure 1 of consumers is distributed uniformly along a unit interval. The incumbent is exogenously located at 0, while entrants are exogenously located at 1. Utility of purchasing the incumbent or the entry product for a consumer in location $x \in (0,1)$ is given by

$$U_b(x) = V_b - p_b - tx$$
$$U_g(x) = V_g - p_g - t(1-x)$$

where t is the travel cost, and $V_g \leq V_b$.

The game proceeds as follows. First, the incumbent sets a price. Next, all potential entrants see the price, and decide whether to enter or not. Entry carries a fixed cost F. Finally, the firms that decided to enter play a Cournot game against the inverse demand curve implied by the pricing decision of the incumbent.[13]

The overall maximization problem of the incumbent is

$$\max_{p_b} p_b \left(D_L(p_b) + D_S\left(p_b, p_g^\star(p_b)\right)\right)$$

[13]The Cournot assumption is made for convenience and because the Cournot model (unlike the Bertrand model) guarantees an inverse relationship between number of firms and markup. A more accurate model could involve randomized locations for biosimilar products, but such a model would become unnecessarily complicated without generating any additional insights.

where

$$D_L(p_b) = \begin{cases} \alpha & \text{if } p \leq V_b \\ 0 & \text{otherwise} \end{cases}$$

and

$$D_S\left(p_b, p_g^\star(p_b)\right) = \min\left\{\max\left\{0, \frac{1}{2} + \frac{V_b - V_g - p_b + p_g^\star(p)}{2t}\right\}, \frac{V_b - p_b}{t}, 1\right\}$$

Demand in the price-sensitive segment is a piecewise function because, for some values of p_b and p_g, the incumbent captures the entire segment (or stays out of it altogether).[14]

2.2 *Equilibrium and Model Predictions*

The segmented nature of the market implies that the incumbent has three options:

1. Capture only the loyal market and stay out of the price-sensitive market
2. Capture the loyal market and compete with the entrant over the price-sensitive market
3. Capture the entire market

The optimal choice depends on t, ΔV, and F.

Equilibrium price and profits are straightforward to calculate for options 1 and 3, which are corner solutions. If the incumbent focuses on the loyal market only, it will set price $p_1 = V_b$, netting profit $\Pi_1 = \alpha V_b$. To capture the entire market instead, the incumbent must set price $p_3 = \Delta V - t$. Doing so nets profit $\Pi_3 = (1-\alpha)\, p_1$. The equilibrium outcome in the competitive case is more complicated, but we show in Appendix B that the optimal price can be written as $p_2 = K(t, F) + \frac{\Delta V}{2}$, where $K(\cdot)$ is a function increasing in both t and F.

[14] See Appendix B.2 for a derivation of the demand function.

Figure 2 displays the optimal price as a function of ΔV for visual clarity. The key result is that, while price is generally increasing with respect to ΔV, a sufficiently low value of ΔV generates a discontinuous jump in price as the incumbent retreats to the loyal segment of the market. The following theoretical results describe the best-response function of the incumbent and the thresholds ΔV_1 and ΔV_2 on the graph.

Proposition 1. *There exist thresholds $\Delta V_1(t)$ and $\Delta V_2(t)$ such that for all $\Delta V < \Delta V_1(t)$, the incumbent sells only to the loyal market, and for all $\Delta V > \Delta V_2(t)$ the incumbent captures the entire market.*

We provide a formal proof of Proposition 1 in Appendix B, and discuss the intuition here. The first part of the proposition depends on the fact that a lower ΔV lowers profits and forces the incumbent to compete more aggressively on price in the price-sensitive market. At some point, the price required to compete will be low enough that it makes more sense to abandon the market altogether, in order to extract the maximum surplus from the loyal segment of the market. The second part of the proposition is equally intuitive. At large enough ΔV, the entrant stops representing credible competition in the price-sensitive market, and the incumbent can capture the entire market without needing to lower the price too much.

The following two Corollaries describe the thresholds ΔV_1 and ΔV_2 as a function of our parameters of interest, t and F:

Corollary 2. $\frac{\partial \Delta V_1}{\partial t} \leq 0, \frac{\partial \Delta V_2}{\partial t} \geq 0$. *There exists a threshold $\bar{t}$ such that for all $t < \bar{t}$, $\Delta V_1(t) = \Delta V_2(t)$.*

Corollary 3. $\frac{\partial \Delta V_1}{\partial F} \leq 0, \frac{\partial \Delta V_2}{\partial F} \leq 0$.

The proof of both Corollaries is also found in Appendix B. The intuition behind the first result is that a decline in travel cost t has two effects. On the one hand, it makes it easier for the entrant to compete and decreases overall profits for the incumbent. This in turn makes it less worthwhile for the entrant to compete in the price-sensitive market, and

increases the chance that the incumbent will stay out of it altogether. On the other hand, the decline in travel cost makes it easier for the incumbent to compete for consumers very close to the entrant. Hence, capturing the entire market becomes a relatively more attractive proposition. The combination of these two effects implies that a fall in t makes option 2 look worse than both option 1 and option 3. At small enough t, option 2 will never be optimal, and the incumbent will either capture the entire market or leave the price-sensitive market to the entrant altogether.

The intuition behind the second result is that a lower fixed cost of entry lowers the minimum profits required for entry. In turn, this implies that the incumbent has to set a lower price in order to discourage rivals from entering the market.[15]

2.3 Welfare and Spending

We conclude by discussing the implications of the model for policy. We note that our model is not necessarily well-suited for classic welfare analysis, for two reasons. First, our assumptions ensure that all demand is satisfied, regardless of the price charged by each firm.[16] This means that the market is always "efficient." Second, demand in the price-sensitive market depends on characteristics (such as ΔV and t) that do not necessarily reflect objective notions of patient well-being. This is because medical evidence suggests (and FDA requirements mandate) that there are virtually no practical differences between biosimilars and their reference biologics, so any perceived difference may not actually translate to a welfare loss (Jørgensen et al., 2017).

Despite these limitations, our model can still speak to prices and spending, which are objects of first-order relevance for policymakers. Moreover, some of the equilibrium outcomes that we derive can also speak indirectly to welfare. For example, the average price paid by consumers will probably matter for access in the real world (though again,

[15]Interestingly, an implication of the model is that $\frac{\partial \Delta V_1}{\partial F} = \frac{\partial \Delta V_2}{\partial F}$, which means that a movement in F results in an equal shift for both.

[16]These assumptions can be relaxed, but not without significantly complicating the derivation of the equilibrium.

not in the version of the model we derive). We show in Appendix B.3 that the average price paid by consumers in the price-sensitive segment of the market is increasing in both ΔV and t. This suggests that reducing ΔV and t (to the extent that it is possible) is a valuable policy goal, and justifies the focus of practitioners and policymakers on fostering the success of biosimilar drugs.[17]

3 Impact of Biosimilar Entry on Price, Volume, and Formulary Placement of Reference Biologics

3.1 Data

To study the impact of biosimilar entry, we construct a comprehensive database of prices, sales, and formulary placement of biologic drugs. We do so by combining four different data sources.

First, we bring in data on list price, net price, and net sales from SSR Health. The SSR Health database covers roughly 1,000 brand drugs and contains quarterly data on Wholesale Acquisition Cost (WAC), net price, and net sales from 2007Q1 to 2020Q2.[18] WAC is an estimate of the price manufacturers charge to wholesalers and large distributors and does not take into account any rebates or discounts. To obtain an estimate of net price, SSR Health divides reported net sales in quarterly earning documents—which are comprehensive of all discounts and rebates—by units sold. This estimate reflects the average revenue earned by the manufacturer for each unit of drug sold and is estimated at the drug-quarter level. We do not observe variation across payers, which means that

[17] We exclude the price paid by patients in the loyal segment because those patients will likely access the drug no matter the price. The average overall price is also decreasing in ΔV and t over the vast majority of the parameter space, but can have a discontinuity around ΔV_1, when the incumbent switches to a high-price strategy focused on the loyal segment only.

[18] SSR Health derives its estimates using data on WAC sales and units sold from Symphony Health, and it collects net sales figures from the SEC filings and other disclosures of publicly-traded companies. For further discussion of the coverage of the SSR Health data, see the data section and Online Appendix A of Feng et al. (2020).

we cannot link changes in prices directly to changes in formulary statuses. Another small downside of this measure is that it includes discounts that do not accrue to payers, such as coupons offered directly to patients (see e.g. Dafny et al., 2017). We also use this data to calculate estimates of units sold by dividing net sales by net price.

To address some of the limitations in our measure of net price, we use Average Sales Price (ASP) as a second source of price information. ASP is a publicly available measure of net price published by the Centers for Medicare and Medicaid Services (CMS).[19] ASP data is available on a quarterly basis starting in 2005. Relative to the measure of net price in the SSR Health data, ASP has the advantage of being calculated using proprietary data provided directly from manufacturer to the government. However, the ASP measure has three drawbacks. First, ASP excludes rebates paid to Part D plans, the Department of Veterans Affairs, and Medicaid, as well as a few other minor exceptions.[20] Second, CMS publishes ASP only for drugs covered by Medicare Part B. As a result, we do not have ASP for drugs available only through retail pharmacies. Third, CMS aggregates ASP at the level of a Healthcare Common Procedure Coding System (HCPCS), which for drugs usually means a molecule. This aggregation has a minimal impact on our sample, which is made up of biologics and on-patent brand drugs. The only exception is insulin, which has a single HCPCS code. Two insulin products in our data experience biosimilar entry, so we must exclude them from the ASP analysis.

Our third data source is formulary coverage data from MMIT Analytics. A formulary is a list of drugs covered by a health insurance plan. Formularies divide drugs into several categories of coverage called tiers. Although tier design can change from plan to plan, most formularies include at least two tiers of brand coverage: a preferred tier for

[19] CMS uses ASP to determine the reimbursement rates for prescription drugs administered in outpatient settings under Medicare Part B.

[20] This exclusion is stated in the *Code of Federal Regulations*: "In calculating the manufacturer's average sales price, a manufacturer must exclude sales that are exempt from inclusion in the determination of the best price under section 1927(c)(1)(C)(i) of the Act" (42 CFR §414.804 (a)(4)(i)). The cited section refers to 42 CFR §447.505, which defines best price for the purposes of Medicaid reimbursement and specifies the exemptions we mention in the main text.

brands that grant higher discounts, and a separate tier for all remaining ones. Drugs in the preferred tier have lower associated copays, while drugs in higher tiers have the higher copays, or, occasionally, coinsurance rates. Formularies can also place non-monetary restrictions on drugs. Two frequent restrictions are Prior Authorization (PA), which requires physicians to submit a written form to the insurer before authorizing a prescription, and Step Therapy (ST), which authorizes using a drug only only after an alternative therapy has failed. The MMIT data contains quarterly snapshots of formulary coverage for a set of 300 drugs from 2011Q1 to 2020Q2 at the drug-health-insurance-plan level. The data cover all health insurance plans in the U.S. across commercial insurance, Medicare, Medicaid, and the ACA health exchanges, for a total of over 300 million covered lives in 2020. Using the MMIT data, we construct three measures of coverage at the drug-year level: the fraction of insured individuals whose formulary offers (i) any coverage, (ii) unrestricted coverage, or (iii) preferred coverage of a given drug.[21]

Fourth, and finally, we collect biosimilar approval and launch dates from the FDA's website and from public announcements by pharmaceutical companies, respectively.

3.2 Empirical Strategy and Summary Statistics

We analyze the impact of biosimilar entry using a generalized difference-in-difference approach. Our main specification is

$$Y_{it} = \alpha_i + \delta_t + \beta \times EventCounter_{it} + \epsilon_{it} \tag{1}$$

where our core sample is the set of all biologic drugs and the "Event Counter" increases for the reference biologic every time a biosimilar enters. Our dependent variables are measures of price, volume sales, and formulary coverage. We control for drug fixed-effects in all regressions, which is important given the large variance in outcomes across

[21] For a more detailed discussion of the MMIT data and how we create these variables, please refer to Appendix A.

drugs. In regressions where the dependent variables measure price or formulary coverage, we also control for year fixed-effects. In regressions where the dependent variable measures volume, we control for age fixed-effects instead.[22] We cluster standard errors at the drug level throughout.

Recent work in the econometrics literature has highlighted several limitations of estimating a two-way fixed effects model and interpreting coefficient on the interaction term (β in our model) as the average treatment effect on the treated (see e.g. Callaway and SantAnna, 2020; Sun and Abraham, 2020; Goodman-Bacon, 2021). To address the issues, we allow for time-varying effects around each biosimilar entry event in robustness checks. Additionally, having a larger number of untreated than treated observations limits the potential bias in Goodman-Bacon (2021), because one of the main concerns is that future treated observations implicitly serve as controls for past treated observations. To partially address these concerns we repeat the analysis with an even larger control group, finding virtually identical results (see Appendix C.1).

Overall, our regressions include ten biologic drugs that experienced biosimilar entry at some point between 2007Q1 and 2020Q2, and 177 other drugs. Table 1 displays basic summary statistics for these two groups. Biologics that experience biosimilar entry tend to have higher average invoice sales and net sales, and slightly better formulary coverage. This is not especially surprising, as biosimilars are more likely to challenge successful products.

3.3 The Impact of Biosimilar Entry on Incumbent Price, Volume, and Formulary Coverage

We start by examining the effect of biosimilar entry on the price, volume, and formally coverage of reference biologics. We use three measures of price. WAC is our measure of

[22] We measure age as years since U.S. launch date. Although controlling for both age and year FE may be preferable, the two sets are highly collinear, and they can lead to overfitting on limited variation in the data. Prices tend to increase over time, while formulary coverage tends to decrease over time, regardless of age. Conversely, volume follows an inverted-U shape, making it more important to control flexibly for age effects.

list price. To measure price net of rebates, we use data from SSR Health as well as ASP data from CMS. We measure volume simply as a count of units sold.[23] The formulary outcomes aim to measure generosity of coverage, and are expressed as the fraction of patients whose health plan offers any coverage, unrestricted coverage, or preferred coverage of a given drug (three measures in total).

Table 2 displays estimates of Equation 1. In Panel A, we find that biosimilar entry is associated with a minimal response in WAC, but a large and significant fall in net price.[24] ASP also drops, but by a lower amount. The different effects on net price and ASP are likely due to the fact that ASP does not incorporate discounts to Medicare Part D, Veteran Affairs, and Medicaid, whose prices (especially the last two) tend to be lower. We also find some noisy evidence that biosimilar entry leads to a fall in volume sales. In Panel B, we report results on the impact of biosimilar entry on incumbents' formulary coverage. We find that biosimilar entry leads to worse formulary coverage. However, the magnitude of the effects are small relative to the baseline rates of coverage presented in Table 1. The biggest change is to the preferred coverage rate, a reduction of about 3.5 percentage points on a baseline of 23 percent. Unrestricted coverage falls 2.1pp on a baseline of 34 percent, and coverage rate falls a noisy 2.5pp on a baseline of 90 percent.[25]

We conduct a series of robustness checks on our main results. Our primary check is to allow for time-varying coefficients by interacting an indicator for each entry event with year fixed effects (measured relative to the entry event). We plot our results in Figure

[23]Units vary across drugs, but this does not matter for our regression because we analyze percentage effects and also control for drug fixed-effects. In one case, the unit of a product (Herceptin) changed in the middle of our sample; the original 440mg unit was replaced by a smaller 150mg unit in 2017Q2. To keep prices consistent, we adjust units by a $^{44}/_{15}$ factor in all years following the change. Herceptin aside, changes in drug units tend to be rare, given that most biologic drugs are only ever available in a single formulation. The units of drugs with multiple formulations can vary slightly as the proportion of sales coming from a certain formulation changes over time. With the exception of Herceptin, this variance leads to minor movements in the data, so we treat it as measurement error.

[24]The phenomenon of WAC, or list price, not falling after a biosimilar enters has been widely reported in the media and may have contributed to skepticism about biosimilars. For example, Atteberry et al. (2019) use the absence of response in WAC after the entry of a filgrastim biosimilar as evidence that biosimilars are ineffective.

[25]We note that, because our formulary data begins in 2011, the results do not reflect the impact of the entry of early biosimilars.

3. Time-varying coefficients allow us to assess whether the core estimates are picking up secular trends and address some of the previously-mentioned concerns raised by the econometrics literature on two-way fixed-effects. The estimates support the idea that incumbents are responding to entry. None of the outcomes display significant pre-trends, and we find a gradually increasing negative response in net price and ASP that plateaus in the long-run.[26] List price exhibits a precisely estimated non-response. We also report the corresponding estimates for formulary outcomes in Appendix Figure 8. Again, the results support the validity of the core regression estimates.

We also provide two additional robustness checks related to concerns about the control group. First, we compare the raw outcomes of drugs that experience biosimilar entry versus other biologics that never experience biosimilar entry. Appendix Figure 9 shows evidence from the raw data that supports the core estimates. Biologics that face biosimilar entry exhibit very similar list price trends to biologics in the control group, but exhibit a significant departure from trend in net price. There are strong pre-trends in units that make it difficult to make a clean comparison between the two groups. Second, we expand the control group to include all other drugs and report the results in Appendix Table 4. We find similar if not stronger results. As we explain in Appendix C, small molecule brands may not serve as an appropriate control group for biologics, because they might have greater incentives to increase net price, which would make biologics look like they are reducing net prices.

Finally, we provide additional evidence on the timing of the incumbent's response. We add an additional event counter that captures when the FDA approves a given biosimilar. As summarized earlier, there have been significant delays between approval and entry for most of the biosimilars in our sample. Potentially, our estimates could be picking up the incumbent's response to approval rather than entry. Appendix Table 5 reports our estimates. We find that approval appears to lead to a small increase in net price, followed

[26] Estimates for long-run response are affected by selection, because our panel is not balanced (i.e., we do not observe a full three years of data for all entry events).

by a drop of 28 percent in net price after entry.

Our robustness checks do not fully address the issue that the set of biologics facing biosimilar entry is selected. However, the most obvious concerns suggest that such selection would lead to a downward bias on the coefficients of interest. That is, we expect biosimilars to enter in markets with relatively higher and faster-growing sales. We can partially control for the level of sales using drug fixed-effects, but we cannot adequately control for future growth. Drugs can have unobservably higher future sales because of growing volume, growing price, or both. Accordingly, any negative impact of biosimilars on the reference biologic's volume and price will be attenuated by the growing path of the market for that molecule, which would lead to a downward bias on our estimated coefficients.

Overall, the response of incumbent biologics to biosimilar entry stands in contrast to that of small-molecule brand drugs to generic competitors, which is to avoid competing on price, and instead cater to a small group of patients with high willingness to pay. This result is consistent with our model of biologic and biosimilar competition and with the idea that perceived quality differences are greater for biosimilars than for generics. Empirical research dating back to the time of the Hatch-Waxman Act has consistently found that brand drugs essentially "acquiesce" to generic entry. Brand prices generally do not change and even increase after generic entry and volume falls by up to 90 percent within the first year of generic competition (Grabowski and Vernon, 1992; Berndt and Aitken, 2011; Grabowski et al., 2016). The average response of incumbent biologics is to reduce prices and maintain volume. Our model suggests the contrasting responses could be driven by greater perceived quality difference between biologics and biosimilars versus brands and generics.

3.4 Suggestive Evidence of Heterogeneous Response to Biosimilar Entry

Our model conjectures that perceived quality differences could be driving the average response of incumbent biologics to biosimilar entry. In particular, we have noted the contrasting responses by incumbent biologics and incumbent brands to copycat entry. To provide a comparison within the set of incumbent biologics, we exploit variation in the approval mechanism of biosimilars created by law changes and regulatory quirks that results in some biosimilars coming to market with a larger body of clinical evidence.

Of all biologics that have experienced biosimilar entry, five are competing against biosimilar products approved through the accelerated channel introduced by the BPCIA, but four are competing against products that used different avenues to approval: Betaseron, Neupogen, Humalog, and Lantus. Our hypothesis is that patients and providers might perceive the difference between these four products and their biosimilars to be smaller. The biosimilars for Betaseron and Neupogen went through the same standard FDA approval process for all biologics, so they reached the market having cleared the same standard of evidence required of their reference biologics. The biosimilars for Humalog and Lantus were approved through an abbreviated pathway called 505(b)(2), which is reserved for follow-on products such as line extensions. Because follow-on products are generally acknowledged to be identical (and sometimes superior) to their originators, the perceived difference between these two products and their biosimilars could also be smaller. Moreover, insulin is also a relatively simple biologic drug, and one that has been available for over a century.

To test the hypothesis we run another set of regressions using time-varying coefficients. Neupogen competed initially against a biosimilar approved through a regular Biologic License Application (Granix), but it also later competed against additional biosimilars approved through the abbreviated procedure. This makes allowing for heterogeneous time-varying responses important to avoid incorrect inferences. Consistent with the predictions of the model, we find some evidence of different responses by incum-

bents facing the drugs approved through non-abbreviated channels.[27] Figure 4 shows price, volume, and formulary coverage trends for biologics whose biosimilars were approved through the accelerated BPCIA procedure vs. biologics whose biosimilars were approved through alternative procedures. The net price and formulary graphs show patterns consistent with our model's predictions. Entry of biosimilars approved through an abbreviated procedure is associated with a steep and significant drop in price, but a small and barely significant drop in formulary coverage. Conversely, it appears that entry of biosimilars approved through non-abbreviated procedures had a small (though noisy) effect on price, and a large and significant drop in coverage.

The volume results are more mixed. We would expect to see a stronger volume reaction among originator biologics exposed to competition from biosimilars approved through non-abbreviated procedures. What we see instead are small and noisy effects in both samples, though we do see a negative and significant drop in volume three years after entry by a biosimilar approved through non-abbreviated procedure. We also note that the coefficients in this sample seem to indicate a positive pre-trend in the lead-up to biosimilar entry. This pre-trend is consistent with selection concerns in this sample (manufacturers of these products *chose* to seek approval even in the absence of an abbreviated pathway), and might make it harder to identify an effect on volume.

We conclude by noting that these results cannot be interpreted as more than suggestive evidence given (i) the extremely small samples; and (ii) the lack of long-term data (especially for the abbreviated pathway products). As more biosimilars are approved, more evidence will be needed to confirm this initial analysis.

3.5 Policy Implications and Future Outlook for Biosimilar Products

We use our model and empirical findings to discuss policy implications and future trends. The two main challenges facing biosimilars are (i) high development costs and (ii) lin-

[27] The model makes an unambiguous prediction on volume, but not on price. As long as $\Delta V > \Delta V_1$, a fall in ΔV leads to a lower price for the incumbent. The price increases only when ΔV falls below ΔV_1.

gering uncertainty about their effectiveness and quality—which in turn allows reference biologics to maintain a dominant position in the market by granting additional discounts. These two issues can interact with one another to create a particularly challenging environment for biosimilars. High development costs limits the number of potential entrants, which in turn makes it more profitable at the margin for reference biologics to maintain a dominant position through strategic discounts and rebates. The converse also applies: if reference biologics can credibly commit to fighting biosimilar entry, the potential profits of launching a biosimilar will be low, further discouraging future candidates.

The U.S. government and the FDA have additional options for tackling these two issues. Policies that aim to lower the cost of developing and launching a biosimilar could target two main sources of cost: the FDA approval process and the risk of potential litigation. The FDA approval process for biosimilars has already been streamlined by the BPCIA. However, the accelerated pathway still requires biosimilars manufacturers to run clinical trials with the goal of showing equivalence with the reference biologic. Although these trials are smaller and cheaper to run than traditional trials for New Drug Applications (NDAs) and Biologic License Application (BLAs), they are often still quite expensive. As more evidence accumulates that biosimilars are indeed broadly equivalent to biologics, the FDA could remove this requirement altogether, perhaps replacing it with a pharmacovigilance requirement for the first few years post-approval.[28] The government could also take steps to limit the exposure of biosimilars to litigation from manufacturers of reference biologic drugs. Indeed, there is already bipartisan legislation in Congress, the Biologic Patent Transparency Act, that would force manufacturers of biologics to register all patents relevant to a given product, akin to the FDA Orange Book for small-molecule drugs. Passing this legislation could reduce legal uncertainties facing potential entrants.

A second set of policies should aim at fostering biosimilar adoption, either by collecting and disseminating evidence of bioequivalence with reference biologics, or by pro-

[28]One possible downside of this policy is that it might contribute to negative perceptions of biosimilar quality.

moting biosimilar use over reference biologics. Policies falling under the first umbrella could subsidize studies comparing the safety and effectiveness of biosimilars and biologics, and/or encourage the spread of such information. One example of a policy falling under the second umbrella is the recently passed Advancing Education on Biosimilars Act.[29] The purpose of this act is to provide the government with avenues through which they can educate providers, patients, and caregivers on biosimilars. Some of the specific resources cited are webinars, websites with the purpose of providing information on safety and development of biosimilars, and interchangeability status of biosimilar products.

Policies to promote biosimilar use could also include favorable government reimbursement policies and mandatory substitution laws. Reimbursement policies for Medicare Part B currently do not favor biosimilar drugs. According to current regulation, biosimilars are reimbursed at the Average Sales Price (ASP), plus 6 percent of the ASP of the reference biologic.[30] In theory, this existing policy provides the same financial incentive to prescribe a biosimilar or its reference biologic. In practice, however, hospitals for which the acquisition cost of biologics is below the ASP will still be inclined to prescribe reference biologics. Consistent with this interpretation of the rule, recent evidence from IQVIA suggests that 340B clinics—which have access to favorable pricing—have lower adoption rates for biosimilars of Bevacizumab (IQVIA, 2020). To incentivize switching to biosimilars, CMS could adopt its policy for small-molecule brand and generic drugs: when a generic drug enters the market, Medicare Part B calculates a molecule-specific sales-weighted ASP, and then uses it to reimburse both brand and generic versions.[31]

[29] See the full text of the act at https://www.congress.gov/117/plaws/publ8/PLAW-117publ8.pdf, retrieved on July 29, 2021.

[30] Until 2018, biosimilars were reimbursed using the standard Part B formula of ASP plus 6 percent. Given that the ASP of biosimilars is generally lower than that of biologics, this policy actually provided an incentive to prescribe the reference biologic over the biosimilar.

[31] A potentially less extreme version of this policy was recently introduced in Congress: HR 6179 would establish a "shared savings" program encouraging physicians to prescribe biosimilars by offering them a percentage of any net realized savings. The bill can be accessed at https://www.congress.gov/bill/116th-congress/house-bill/6179?s=1&r=5, retrieved November 13, 2020.

Finally, we note that these problems might slowly resolve themselves over time, even in the absence of government intervention. Current medical evidence strongly suggests that biologics and biosimilars are basically identical (see e.g. Barbier et al., 2020; Luttropp et al., 2020). At the same time, public awareness of biosimilars among both patients and physicians appears to be low: according to recent polls, 65 percent of Americans are not familiar with the term "biosimilars", while around 40 percent of physicians do not believe that biosimilars are equivalent to originator biologics—despite this being the requirement for FDA approval.[32] As knowledge spreads to physicians and patients, we can expect insurers and providers to promote biosimilar switching more aggressively.[33] This learning process occurred with generics as well. Early evidence of generic adoption suggests that brand drugs were able to maintain significant market share even one or two years after generic entry (Grabowski and Vernon, 1992). Today, this is no longer the case, as generics capture almost the entire market within a few months (Grabowski et al., 2016). Policies targeted towards greater acceptance of biosimilars may speed up this process.

4 Conclusion

In this article, we have examined how manufacturers of biologic drugs react to the entry of biosimilar competitors. We find that, so far, the average reaction has been to compete on price with these new entrants. By cutting prices, reference biologics have been able to limit losses in volume and formulary coverage, in turn contributing to the slow uptake of biosimilars highlighted by many recent reports (see, e.g., IQVIA Institute for Human Data Science, 2020).

The main conceptual question that arises from this result is why reference biologics do not behave more like small-molecule brand drugs, which rarely compete on price

[32] For poll results, see harrisx.com/wp-content/uploads/2020/03/Biosimilars-topline-poll-public-memo-VF.pdf, retrieved November 13, 2020, and Cohen et al. (2016).

[33] This is already happening in some contexts, such as Kaiser Permanente in California (https://biosimilarsrr.com/2019/11/07/how-did-kaiser-permanente-reach-95-utilization-of-biosimilar-herceptin-and-avastin-so-quickly/, retrieved November 10, 2020).

with generic drugs. We conjecture that perceived differences in the quality of biosimilar drugs can soften competition in the market, making it relatively more profitable for biologics to compete on price. We use the term perceived because the medical evidence on biosimilars has so far suggested that biosimilars are just as safe and effective as their reference biologics. We exploit regulatory variation to support our claim: biosimilars that receive approval after undergoing more rigorous safety testing do not elicit a strong price reaction from reference biologics.

Our exercise has two takeaways. First, widespread dissemination of information about the safety and efficacy of biosimilars should increase their competitiveness in the market, and eventually convince reference biologics to "acquiesce" to biosimilar entry. Second, even in the absence of such nudges, we expect that—as providers and patients become more familiar with biosimilars—incumbent biologics will react to biosimilar entry by ceding market share and pricing to the less price-sensitive part of the demand curve. Hence, we expect that, in the long-run, biosimilars will be able to approximate the market impact that generics currently have, bringing the BPCIA closer to its stated goal.

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Table 1: Summary Statistics for Treatment and Control Groups

	Biologics w/ Biosimilar		Control Group	
	Mean	Median	Mean	Median
# of Drugs sales data	10		177	
Yearly Invoice Sales (million USD)	3569.28	1295.93	888.15	221.59
Yearly Net Sales (million USD)	1701.42	938.50	737.29	267.70
# of Drugs formulary data	10		86	
Percent Covered	0.89	0.92	0.85	0.88
Percent Unrestricted	0.38	0.32	0.43	0.42
Percent Preferred	0.27	0.17	0.18	0.11

Figures refer to the average value over the years 2007 through 2019.

Table 2: Impact of biosimilar entry on price and volume of biologics

Panel A: Price and Volume

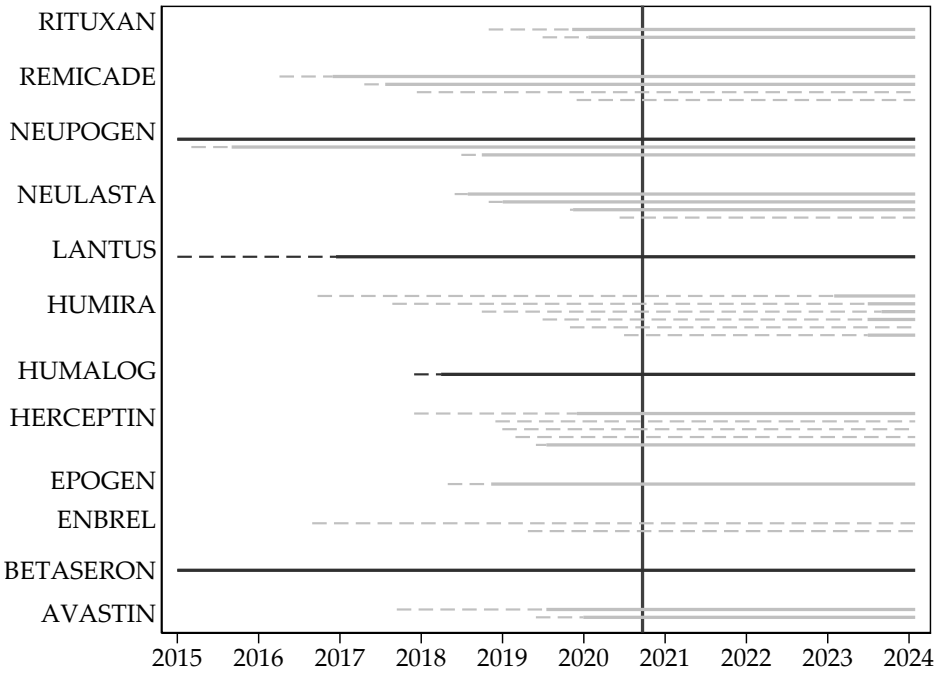
	Log(WAC)	Log(Net)	Log(ASP)	Log(Units)
Biosimilar Entry Counter	0.032	-0.173	-0.062	-0.058
	(0.049)	(0.065)	(0.039)	(0.130)
Drug FE	x	x	x	x
Year FE	x	x	x	
Age FE				x
N	1,438	1,438	596	1,434
Adjusted R^2	0.989	0.945	0.996	0.929

Panel B: Formulary Coverage

	Frac. Pref.	Frac. Unrestr.	Frac. Covered
Biosimilar Entry Counter	-0.0385	-0.0179	-0.0296
	(0.0143)	(0.0101)	(0.0193)
Drug FE	x	x	x
Year FE	x	x	x
N	588	588	588
Adjusted R^2	0.912	0.900	0.787

Notes: Standard errors are clustered at the drug level.

Figure 1: Biosimilar Approval and Launch Timeline



Note: Dashed lines represent approved biosimilars. Solid lines represent launched biosimilars (including predicted future launches based on existing agreements). Biosimilars represented by light-shaded lines were approved through BPCIA's abbreviated pathways, while those represented by dark-shaded lines were approved through a different process. The vertical line indicates July 2020, which is when the data is current.

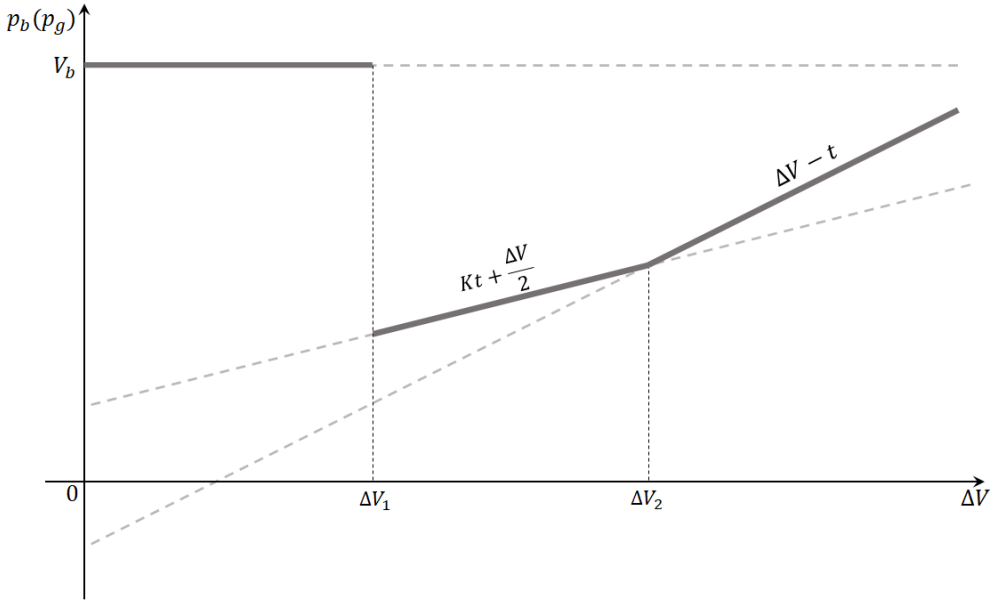
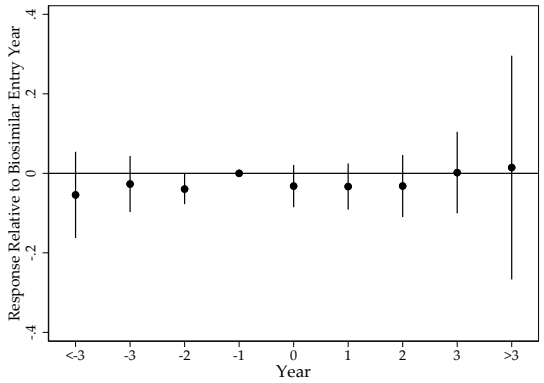
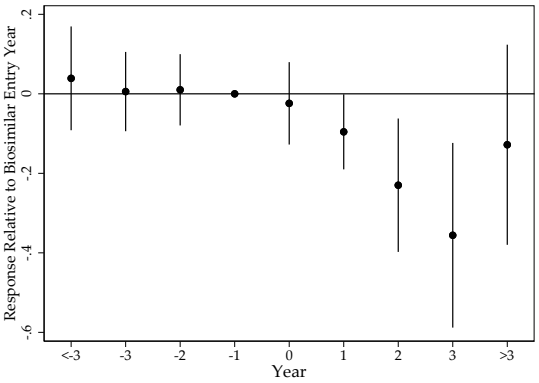


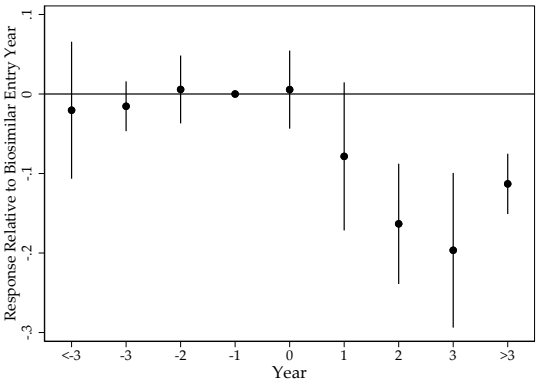
Figure 2: Optimal price of the incumbent as a function of ΔV



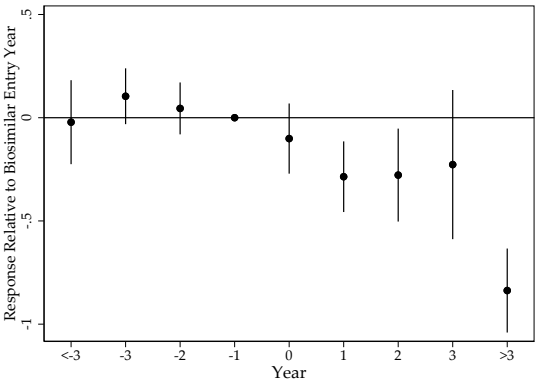
(a) Log(WAC)



(b) Log(Net)

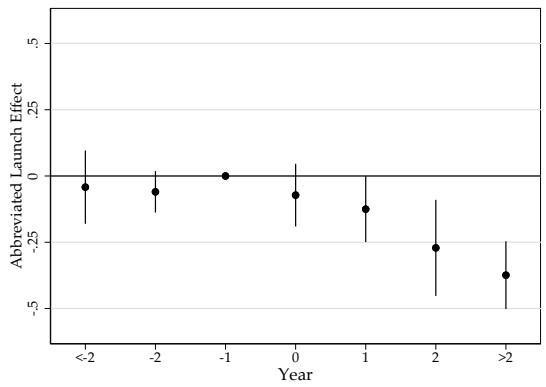


(c) Log(ASP)

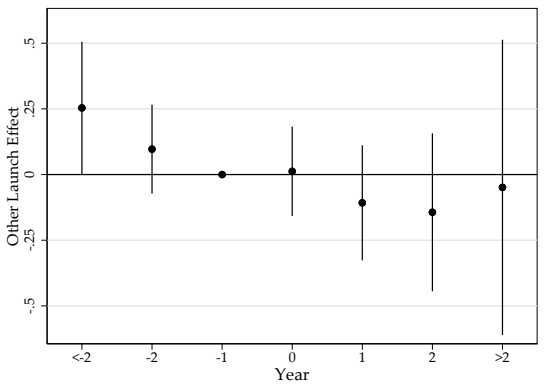


(d) Log(Units)

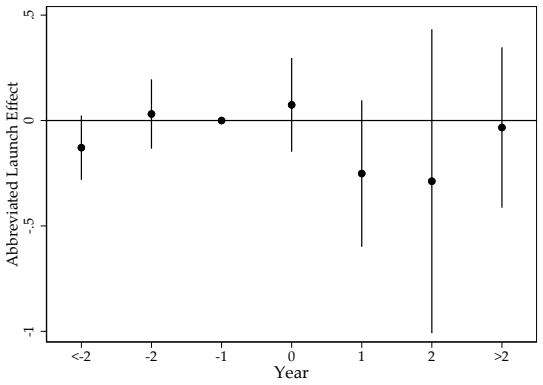
Figure 3: Time-Varying Coefficient Estimates (Price and Units)



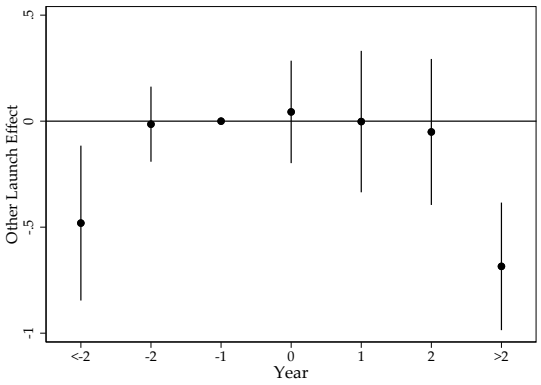
(a) Net Price (Abbr.)



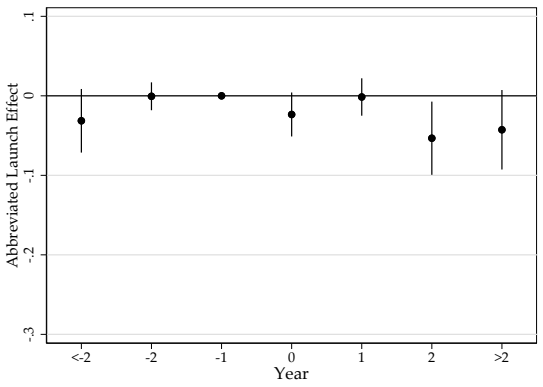
(b) Net Price (Other)



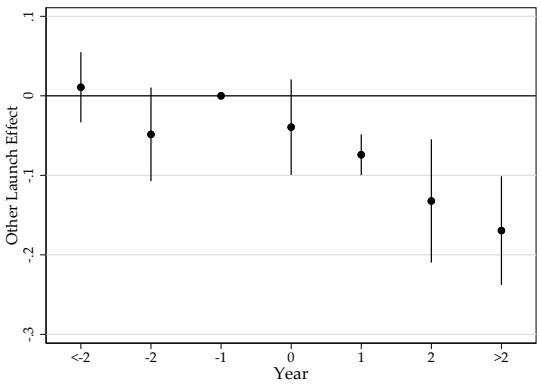
(c) Units (Abbr.)



(d) Units (Other)



(e) Covered (Abbr.)



(f) Covered (Other)

Figure 4: Comparison of reference biologic responses: Abbreviated vs. non-Abbreviated biosimilars

A Data

In this section we describe the formulary data we obtained from MMIT Analytics, and explain how we constructed the coverage variables from that data. For a description of the SSR Health data, see instead Online Appendix A to Feng et al. (2020), particularly Section A.1.

A.1 Formulary Data

MMIT Analytics collects monthly data on formulary coverage from health plans. This data includes information about the coverage tier of a specific drug, as well as the plan sponsor, and the number of lives it covers.

We have data on over 600 drugs—including all biosimilars and reference biologics—from January of 2011 until April of 2020. Throughout this period, MMIT's coverage grew from around 100 million lives to over 300 million lives, representing almost the entirety of the insured U.S. population. The data includes health plans across all possible channels: commercial plans, Medicare, Medicaid (both State-sponsored and Managed Medicaid), as well as the ACA health exchanges (Figure 5).[34]

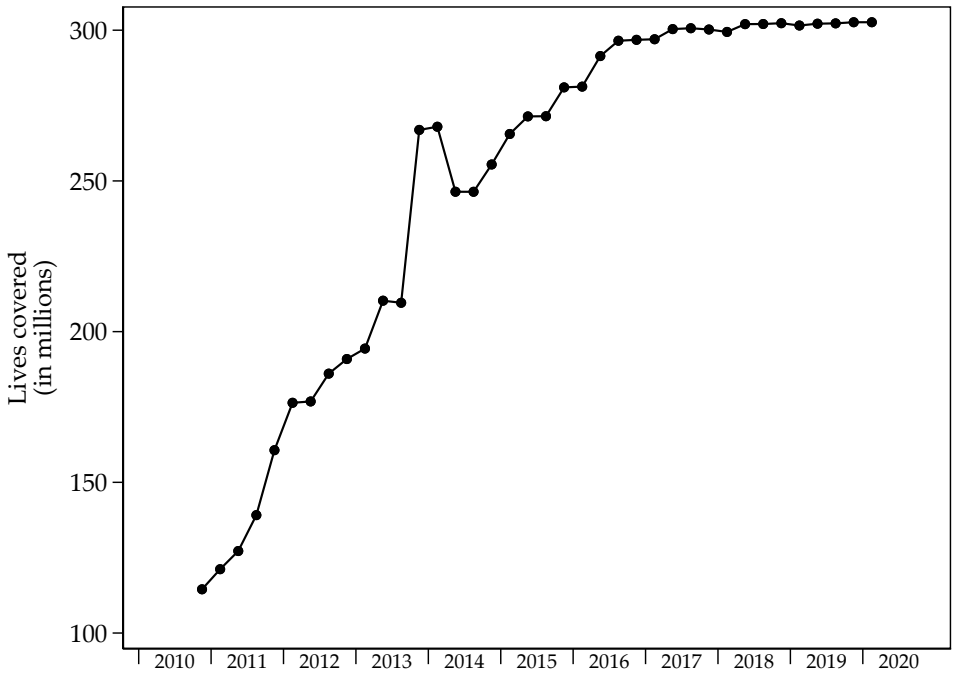
A.2 Construction of coverage variables

MMIT analytics processes the tier information for all formularies to create a harmonized "universal status" variable that describes each formulary's tiers in a way that makes them comparable across plans and years. Moreover, each drug is flagged for three possible non-monetary restrictions: Prior Authorization (PA), Step Therapy (ST), and Quantity Limit (QL). Of these three, only the first two represent meaningful obstacles to the prescription of a drug.[35] We use these two variables to create indicators for three levels of coverage:

[34]The spike in 2014Q1 and 2014Q2 is caused by double-counting of lives in certain (unidentifiable) commercial plans. The issue does not affect other quarters.

[35]Quantity limit refers to the maximum number of doses that can be prescribed, and is used to prevent abuse of medications like opioids—e.g Vicodin or Oxycontin —or amphetamines—e.g. Adderall or Ritalin.

Figure 5: MMIT lives covered



any coverage, unrestricted coverage, and preferred coverage. Table 3 shows how we map the universal status variable to our indicators for any coverage and preferred coverage. Additionally, we consider all drugs that are flagged for PA or ST as "restricted", which in turn defines our unrestricted variable.[36]

The dependent variables in our formulary regressions are weighted averages (using number of lives covered as weights) of these three indicators for each drug and year, across all health plans. Another way to interpret them is as the percentage of lives with a certain level of coverage for a given drug.

B Model Derivation

In this section we provide a full derivation of our model. Section 2.1 in the main text provides the setup.

[36] In the rare cases when a "preferred" drug is flagged for PA or ST, we set the preferred coverage indicator to 0. Missing values (also rare) are considered not covered.

Table 3: Drug tiers assignment

Universal Status	Any coverage	Preferred coverage
Not Covered Drugs Tier	0	0
Unknown Coverage	0	0
Medical	1	0
Injectable Drugs Tier	1	0
Non-Preferred Specialty Drugs Tier	1	0
Specialty Drugs Tier	1	0
Covered Drugs Tier	1	0
Non-Preferred Brand Drugs Tier	1	0
Non-Preferred Generics and Non-Preferred Brands	1	0
Preferred Specialty Drugs Tier	1	1
Generic Drugs Tier	1	1
Non-Preferred Generic Drugs Tier	1	1
Non-Preferred Generics and Preferred Brands	1	1
Preferred Brand Drugs Tier	1	1
Preferred Generic Drugs Tier	1	1
Preferred Generics and Preferred Brands	1	1
Value Brand Drugs Tier	1	1
Value Generic Drugs Tier	1	1
Zero Co-pay Tier	1	1

We assume that demand for the originator product in the price-sensitive market segment follows a Hotelling model. Consumers are indexed by i and distributed uniformly along the unit line. A consumer with location x_i earns

$$U_{ij} = V_j - p_j - t \times |x_i - y_j|$$

from consuming product j, where y_j is the location of the product, V_j is its value, and p_j its price. We use the index b to denote the incumbent, branded product. And the subscript g to denote the entrant, generic (or biosimilar) product.

We make the following assumptions on model parameters:

- $V_b \geq V_g$. This simply ensures that the generic follower cannot be perceived a strictly better than the originator, just as its equal.
- $V_g > t$. This ensures that all consumers would prefer the generic to the outside option if the generic had a price of 0.
- The incumbent and the brand products are respectively located at $y_b = 0$ and $y_g = 1$.

Figure 6 provides a graphical representation of the model.

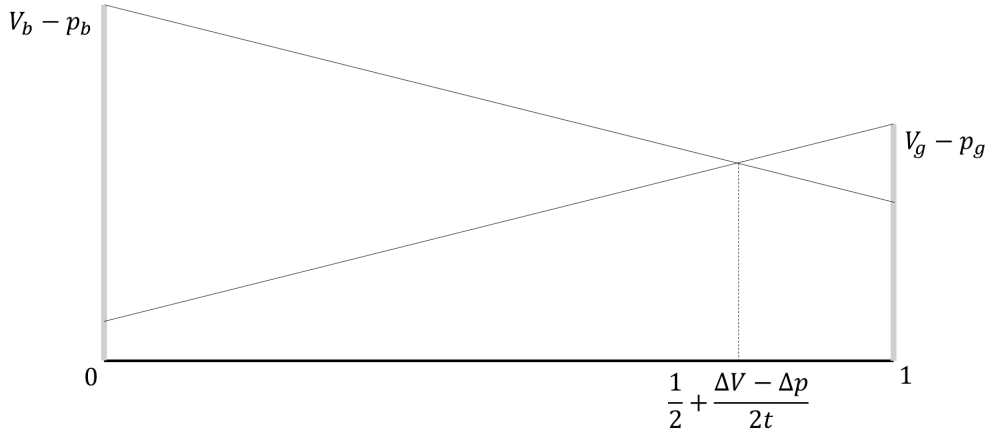


Figure 6: Hotelling model setup for the price-sensitive segment

Finally, we assume that prices are announced sequentially, with entrants announcing their price after observing the price of the originator incumbent.

B.1 Problem of the entrants

The game proceeds as follows. First, the incumbent sets a price. Next, all potential entrants see the price, and decide whether to enter or not. Entry carries a fixed cost F. Finally, the firms who decided to enter play a Cournot game against the inverse demand curve implied by the pricing decision of the incumbent. We solve this game using backward induction.

We start by writing down the demand function faced by the entrants.

Characterization of the demand function

As long as the incumbent remains competitive in the market (i.e. as long as p_b is set such that there exist a consumer with location $x \in (0,1)$ who is indifferent between the incumbent and the entrant, and prefers both to the outside option), the entrants face residual demand function

$$Q\left(p_g\right) = \max\left\{\frac{1}{2} - \frac{V_b - V_g - p_b + p_g}{2t}, 0\right\}$$

If instead the incumbent is not competitive (i.e. p_b is such that the marginal consumer for the entrant is indifferent between the entrant and the outside option), the residual demand function is

$$Q\left(p_g\right) = \min\left\{\frac{V_g - p_g}{t}, 1\right\}$$

Combining the two, we can write the overall demand function as

$$Q\left(p_g\right) = \min\left\{\max\left\{0, \frac{1}{2} - \frac{V_b - V_g - p_b + p_g}{2t}\right\}, \frac{V_g - p_g}{t}, 1\right\} \tag{2}$$

Solution with a competitive incumbent

If the incumbent is competitive, and assuming an interior solution, the inverse demand function is

$$p_g = p_b - \Delta V + t - 2Qt \tag{3}$$

Each entrant then solves

$$\max_{Q_j} Q_j \times \left(p_b - \Delta V + t - 2tQ_j - 2tQ_{-j}\right)$$

The FOC of this problem is

$$\left[Q_j\right] : p_b - \Delta V + t - 2tQ_j - 2tQ_{-j} - 2tQ_j = 0$$

and implies

$$Q_j = \frac{p_b - \Delta V + t - 2tQ_{-j}}{4t}$$

Since each firm is symmetric, $Q_{-j} = (N-1)\,Q_j$. Use this substitution to get

$$Q_j = \frac{1}{N+1} \times \frac{p_b - \Delta V + t}{2t} \tag{4}$$

This, in turn, implies that the price charged by each firm is

$$P = \frac{1}{N+1} \times (p_b - \Delta V + t) \tag{5}$$

Solution with a non-competitive incumbent If the incumbent is not in the market, the inverse demand function is given by

$$Q = \frac{V_g - P}{t}$$

which implies

$$P = V_g - tQ$$

Hence, the problem of each firm is

$$\max_{Q_j} Q_j \times \left(V_g - tQ_j - tQ_{-j}\right)$$

the FOC yields

$$\left[Q_j\right] : V_g - tQ_j - tQ_{-j} - tQ_j = 0$$

which implies

$$Q_j = \frac{V_g - tQ_{-j}}{2t}$$

Since each firm is symmetric, $Q_{-j} = (N-1)\, Q_j$. Make the substitution to get

$$Q_j = \frac{1}{N+1} \times \frac{V_g}{t} \tag{6}$$

Which in turn implies that the price charged by each firm is

$$P = \frac{V_g}{N+1} \tag{7}$$

Entry stage

Before choosing quantities, potential entrants have to decide whether to enter the market or not. Given a fixed cost of entry F, the number of entrants is determined by the maximum number of firms that can enter while still earning positive profits. For simplicity, we treat N as if it were a continuous parameter, so N is pinned down by an exact zero profit condition.

The profit function has two arms, depending on whether the incumbent is competing

or not:

$$\Pi_j(N) = \begin{cases} \frac{1}{2t} \times \left(\frac{p_b - \Delta V + t}{N+1}\right)^2 & \text{if incumbent competitive} \\ \frac{1}{t} \times \left(\frac{V_g}{N+1}\right)^2 & \text{if incumbent not competitive} \end{cases} \tag{8}$$

The number of firms entering is $N^\star$ such that $\Pi_j(N^\star) = F$. If the incumbent is competitive

$$N^\star = \frac{p_b - \Delta V + t}{\sqrt{2tF}} - 1 \tag{9}$$

while if the incumbent is not competitive,

$$N^\star = \frac{V_g}{\sqrt{tF}} - 1 \tag{10}$$

These results imply that the equilibrium demand and price in the Cournot market when the incumbent is competitive are (from Equations 4 and 5):

$$\begin{aligned} Q_j &= \frac{1}{\frac{p_b - \Delta V + t}{\sqrt{2tF}}} \times \frac{p_b - \Delta V + t}{2t} \\ &= \frac{\sqrt{2tF}}{p_b - \Delta V + t} \times \frac{p_b - \Delta V + t}{2t} = \sqrt{\frac{F}{2t}} \end{aligned}$$

and

$$\begin{aligned} p_g &= \frac{1}{\frac{p_b - \Delta V + t}{\sqrt{2tF}}} \times (p_b - \Delta V + t) \\ &= \sqrt{2tF} \end{aligned}$$

When the incumbent is not competitive, quantity and price (from Equations 6 and 7) are

$$Q_j = \frac{1}{\frac{V_g}{\sqrt{tF}}} \times \frac{V_g}{t} = \sqrt{\frac{F}{t}}$$

and

$$p_g = \sqrt{tF}$$

We notice two interesting implications of these results. First, prices are lower in the price-sensitive market if the originator biologic does not compete. This is a consequence of the Hotelling assumptions. When the incumbent is present, the entrants focus on consumers that are "closer" to them in the Hotelling space, so they charge higher prices. When the incumbent is no longer present, firms compete also for customers that are further away and to do so they have to lower their prices.

Second,the equilibrium $P^\star$ and $Q_j^\star$ in the price-sensitive market only depend on whether the incumbent chooses to compete, *not* on the exact choice of a price.[37] This helps us simplify the analysis of the incumbent problem.

B.2 Problem of the incumbent

The demand function of the incumbent in the price-sensitive segment is analogous to that of the entrant:

$$D_b\left(p_b\right) = \min\left\{\max\left\{0, \frac{1}{2} + \frac{V_b - V_g - p_b + p_g^\star}{2t}\right\}, \frac{V_b - p_b}{t}, 1\right\}$$

We then assume that the loyal segment of the market has a measure α of consumers, who are willing to pay up to V_b in order to purchase the product. Hence

$$D\left(p\right) = \begin{cases} \alpha & \text{if } p \leq V_b \\ 0 & \text{otherwise} \end{cases}$$

The incumbent has three options:

1. It can set the maximum price that allows it to capture the entire measure of consumers $1 + \alpha$

[37] Of course Q (the total quantity produced by all the entrants) will depend on p_b through N.

2. It can set a price that is competitive in the price-sensitive market (meaning it will split that market with the entrant)

3. It can sell only in the loyal market, and surrender the entire price-sensitive market to the entrant.

We explore each option separately, leaving option 2 for last, as it is the most complicated one.

Option 1: capture all demand

Because we have already calculate the best-response function of the entrant, we know that the maximum price that allows the incumbent to capture the entire market is $p_b = \Delta V - t + \sqrt{2tF}$.[38] Any price higher than that will allow the entrant to cut into the demand of the incumbent. If the incumbent sets $p = \Delta V - t + \sqrt{2tF}$, it earns profits

$$\Pi_b\left(\Delta V - t\right) = \left(\Delta V - t + \sqrt{2tF}\right) \times (1 + \alpha) \tag{11}$$

Option 3: Pricing to the loyal market only

To extract the maximum surplus from the loyal market, the incumbent should set $p_b = V_b$, yielding profits

$$\Pi_b\left(V_b\right) = \alpha V_b$$

Notice that for $p_b = V_b$ there will never be any profits from the price-sensitive market because no consumers in that market are willing to pay V_b.

Option 2: Pricing to both markets

Now let's calculate the optimal price when pricing to both markets. Since the incumbent is competing $p_g^\star = \sqrt{2tF}$, as previously derived. Hence, we can write the maximization

[38] The price can be higher than simply $\Delta V - t$ because the entrants will charge a minimum price of $\sqrt{2tF}$

problem as

$$\max_p p \times \left(\alpha + \frac{1}{2} + \frac{\Delta V - p + \sqrt{2tF}}{2t} \right)$$

The FOC yields

$$[p] : \alpha + \frac{1}{2} + \frac{\Delta V - p + \sqrt{2tF}}{2t} - \frac{p}{2t} = 0$$

which implies

$$p_b^\star = t\left(\alpha + \frac{1}{2}\right) + \frac{\Delta V}{2} + \sqrt{\frac{t}{2}F}$$

The profits of the incumbent at this equilibrium price are given by

$$\Pi_b = \frac{1}{2t}\left(t\left(\alpha + \frac{1}{2}\right) + \frac{\Delta V}{2} + \sqrt{\frac{t}{2}F} \right)^2$$

B.3 Comparative Statics of the Equilibrium Response of the Incumbent

We now discuss how equilibrium prices change as a function of the underlying parameters of the model.

Impact of ΔV on the best-response of the incumbent

We start by discussing how the best response of the incumbent changes as ΔV changes. Throughout this section we will hold t constant and assume that it is strictly positive.

The optimal strategy of the incumbent depends on which of the three options available yields the highest profits. While the profit from selling to the loyal segment only is fixed, the profit for competing in the price-sensitive market is decreasing in ΔV. Hence, there will be a value of ΔV below which competing is no longer optimal. This point is given by ΔV_1 such that

$$\alpha V_b = \frac{1}{2t}\left(t\left(\alpha + \frac{1}{2}\right) + \frac{\Delta V}{2} + \sqrt{\frac{t}{2}F} \right)^2$$

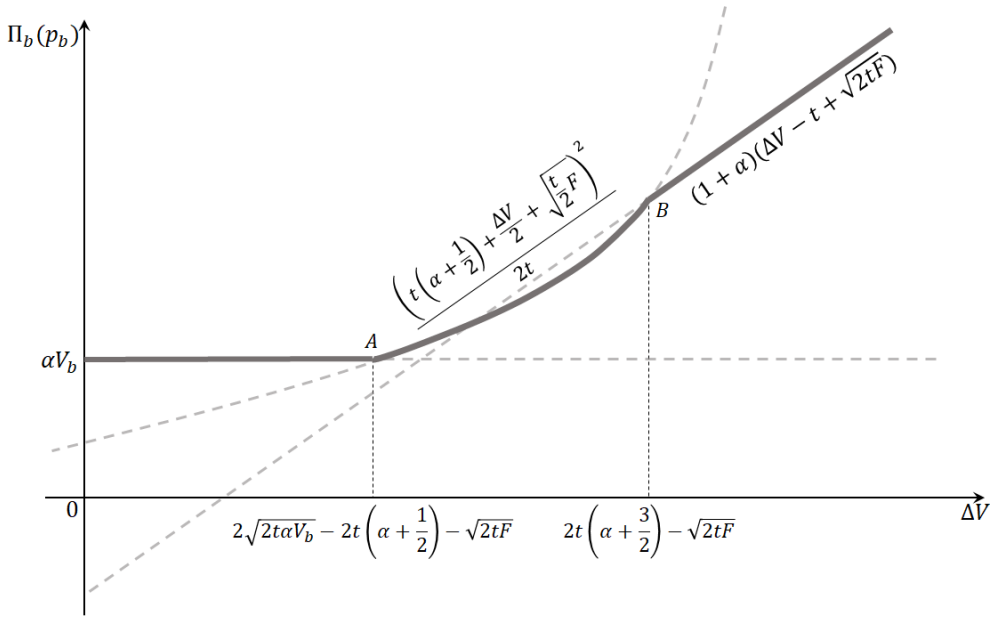


Figure 7: Incumbent profits as a function of ΔV

which implies

$$\Delta V_1 = 2\sqrt{2t\alpha V_b} - 2t\left(\alpha + \frac{1}{2}\right) - \sqrt{2tF}$$

The value of ΔV such that the incumbent captures the whole market is given by ΔV_2 such that demand is equal to 1:

$$\Delta V_2 = 2t\left(\alpha + \frac{3}{2}\right) - \sqrt{2tF}$$

As ΔV increases, the incumbent is more likely to enter and compete in the market.Figure 7 displays the profits of the incumbent graphically for intuition. As ΔV decreases, the incumbent is slowly driven out of the price-sensitive market and into the loyal market.

The two thresholds in the figure map to ΔV_1 and ΔV_2 in Proposition 1. Hence, the derivation in this section serves as the proof of that Proposition.

Impact of t on the best-response of the incumbent

We can then prove Corollary 2 by simply checking how changing t would affect the two thresholds ΔV_1 and ΔV_2.

A fall in t has two effects. First, it makes it easier for the entrant to compete and decreases overall profits, which increases the minimum threshold ΔV that makes it worthwhile for the entrant to compete in the price-sensitive market. This is reflected in the graph by the fact that the intersection point A shifts right whenever t falls (because the expression denoting its x coordinate is unambiguously decreasing in t). Second, however, it makes it easier for the incumbent to compete for consumers that are very close to the entrant. Hence, capturing the entire market becomes a relatively more attractive proposition. This is reflected in the graph by the fact that the intersection point B shifts left whenever t falls (because the expression denoting its x coordinate is unambiguously increasing in t). This proves Corollary 2.

The combination of these two effects implies that for t small enough the incumbent will either capture the entire market, or leave the price-sensitive market to the entrant altogether. Which option is better depends on ΔV.

Impact of F on the best-response of the incumbent Finally, we look at how F affects the equilibrium. This is a straightforward exercise: a fall in F increases the number of potential entrants, which leads to lower prices in the price-sensitive market. In turn, this makes the incumbent less likely to compete for those consumers. This effect is reflected by the fact that both $\frac{\partial \Delta V_1}{\partial F} < 0$ and $\frac{\partial \Delta V_2}{\partial F} < 0$.

B.4 Implications for Welfare

As mentioned in the main text, this model is not well-suited for classic welfare analysis, so we focus on the average price in the price-sensitive segment.The average molecule price

in the market can be written as

$$\bar{p}_S = \begin{cases} \sqrt{tF} & \text{if } \Delta V < \Delta V_1 \\ Q_b\left(p_b^\star\right) \times p_b^\star + \left(1 - Q_b\left(p_b^\star\right)\right)\sqrt{2tF} & \text{if } \Delta V \in [\Delta V_1, \Delta V_2] \\ \Delta V - t + \sqrt{2tF} & \text{if } \Delta V > \Delta V_2 \end{cases}$$

where the first arm is the price charged in equilibrium by biosimilar entrants when the incumbent does not compete,

$$Q_b\left(p_b^\star\right) = \frac{1}{2} + \frac{\Delta V - p_b^\star + \sqrt{2tF}}{2t}$$

is the demand function, and

$$p_b^\star = t\left(\alpha + \frac{1}{2}\right) + \frac{\Delta V}{2} + \sqrt{\frac{t}{2}F}$$

is the price charged by the incumbent in equilibrium when competing on the price-sensitive market.

The comparative statics of this price with respect to ΔV, t, and F are can look a bit tricky to sign, because they depend on a comparison between the price charged by the incumbent and the price charged by the entrant in the middle case, but we can show that, in most relevant cases, the sign of these comparative statics is clear.

Average price as a function of ΔV

We know that the entrant increases its price as ΔV increases (from $\sqrt{tF}$ to $\sqrt{2tF}$), and so does the incumbent ($p_b^\star$ is an increasing function of ΔV and it is equal to $\Delta V - t + \sqrt{2tF}$ for $\Delta V = \Delta V_2$). Moreover, we also know that, at least initially, the price of the incumbent is higher than the price charged by the entrant, because $p_b^\star \approx \Delta V - t + \sqrt{2tF} > \sqrt{2tF}$. At

the lower bound ΔV_1, the price is equal to $\sqrt{2t\alpha V_b}$, which could be lower than $\sqrt{tF}$ if

$$F > 2\alpha V_b$$

Hence, $F < 2\alpha V_b$ is a sufficient condition for $\frac{\partial \bar{p}}{\partial \Delta V} > 0$ (i.e. price increases with ΔV).

Average price as a function of t

In cases when $\Delta V > \Delta V_2$, the price is actually decreasing as a function of t. However, this is a less relevant case, because it implies that no entrant is active in the market. In the two other cases, all prices are an unequivocally increasing function of t. Moreover, the threshold ΔV_1 is a decreasing function of t, which means that as t increases prices go up in each arm, and the lowest arm is harder to attain. These two facts combined imply that $\frac{\partial \bar{p}}{\partial t} > 0$.

Average price as a function of F

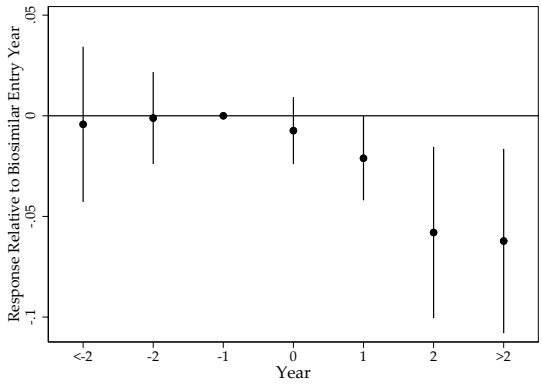
The same argument we made for t also holds for F—it also holds for the third arm. Hence, $\frac{\partial \bar{p}}{\partial F} > 0$.

C Robustness Checks and Additional Results

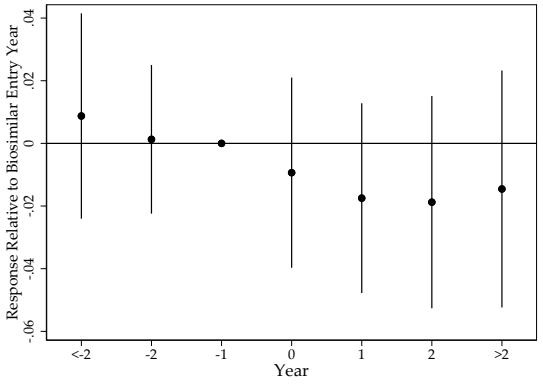
C.1 Robustness Checks

Time-Varying Estimates for Formulary Outcomes

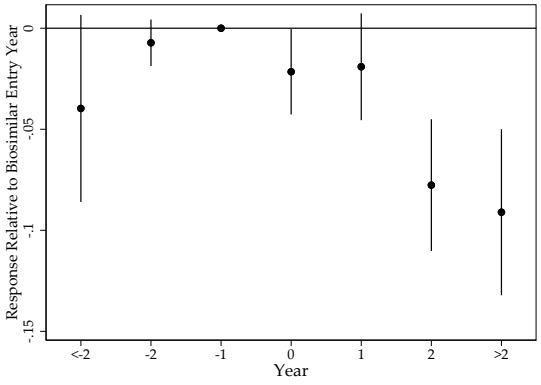
Figure 8 presents evidence on the time-varying response of formulary coverage of incumbent biologics to biosimilar entry. Preferred coverage rates decline over time after biosimilar entry. We find much noisier and smaller point estimates for unrestricted coverage rates. We also find some evidence of long-run impacts on coverage rates. Overall,



(a) Fraction Preferred



(b) Fraction Unrestricted



(c) Fraction Covered

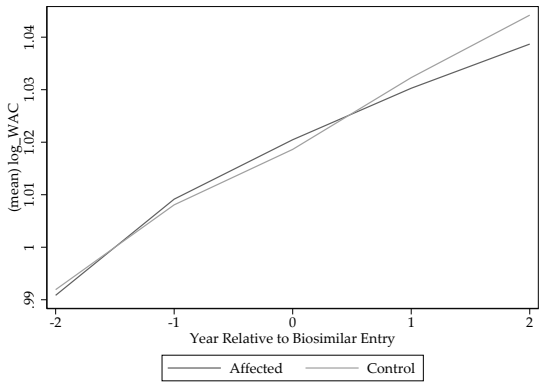
Figure 8: Time-Varying Coefficient Estimates (Formulary Coverage)

the results suggest that there is a small but significant impact of biosimilar entry on the formulary coverage of incumbent biologics.

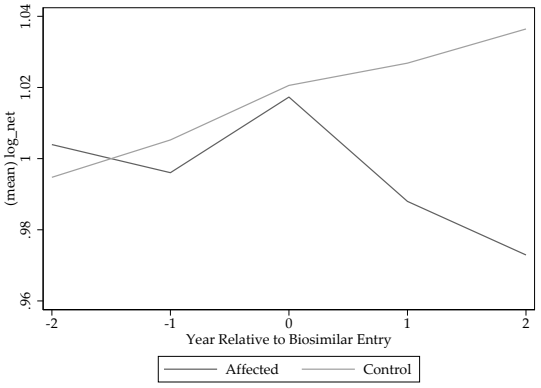
Comparison of Raw Outcomes

Next, we compare raw outcomes between biologics that face biosimilar entry at some point in the sample period versus biologics that never face entry. Specifically, for each biosimilar entry event, we construct a control group consisting of all biologics that never face biosimilar entry and that we have data for in the two year before and two years after the year of entry. We assign these control drugs

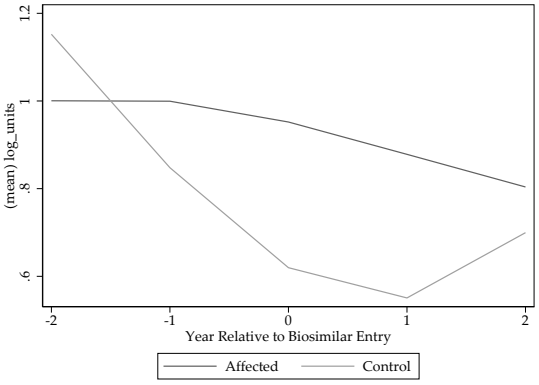
We then average raw outcomes for all treated biologics and for all control drugs by year relative to biosimilar entry and plot them in Figure 9. For visual comparison pur-



(a) Log(WAC)



(b) Log(Net)



(c) Log(Units)

Figure 9: Raw Comparisons Between Treated and Control Biologics

poses, we normalize the sum of the outcomes in relative years -2 and -1 to be the same in treated and control groups. The raw comparisons reflect the core estimate that there is very little response in list price to biosimilar entry. WAC grows at similar rates in the two groups. Net price exhibits a very different pattern. After biosimilar entry, the treatment group experiences a drop in net price, while the control group maintains a steady growth in net price. Finally, we see that units have very different pre- and post- trends between the two groups, making it difficult to identify a precise units response.

Alternative Control Group

We check whether price, volume, and formulary results are sensitive to the sample of drugs we used by estimating our model from 1 on all branded drugs. The set of all

branded drugs might not serve as the best control group for biologic drugs, because of the different post-LOE regime facing small molecule drugs. For example, knowing that generics will take over most of the market after LOE, the manufacturer of branded small-molecule drugs may choose to increase prices significantly to "harvest" existing loyal consumers before LOE. Biologic drugs may not face as clear an incentive to increase prices as much.

Table 4 reports our estimates. We generally find similar and slightly larger negative price responses. In particular, WAC exhibits a negative response after biosimilars enter the market. Overall, the results paint a similar picture to that of the core estimates, and the differences could reflect comparability issues between biologic and small molecule price dynamics.

Table 4: Impact of biosimilar entry on price and volume of branded drugs

Panel A: Price and Volume

	Log(WAC)	Log(Net)	Log(ASP)	Log(Units)
Biosimilar Entry Counter	-0.081	-0.231	-0.077	0.178
	(0.036)	(0.052)	(0.038)	(0.144)
Drug FE	x	x	x	x
Year FE	x	x	x	
Age FE				x
N	7,071	7,071	1,229	7,068
Adjusted R^2	0.987	0.953	0.994	0.928

Panel B: Formulary Coverage

	Frac. Pref.	Frac. Unrestr.	Frac. Covered
Biosimilar Entry Counter	-0.0696	-0.0559	-0.0454
	(0.0160)	(0.0084)	(0.0196)
Drug FE	x	x	x
Year FE	x	x	x
N	2,984	2,984	2,984
Adjusted R^2	0.880	0.894	0.719

Notes: Standard errors are clustered at the drug level.

C.2 *Response to Biosimilar Approval*

As noted in the main text, there are often significant delays from approval to launch of biosimilars. In Table 5, we include an indicator for whether the biosimilar has been approved, in order to test whether incumbents respond to the approval of biosimilars. We find a small increase in net price after approval, followed by a steep drop after biosimilar entry. Potentially, this could reflect some anticipation by the incumbent.

Table 5: Approval placebo test results

	Log(WAC)	Log(Net)	Log(ASP)	Log(Units)
Biosimilar Entry Counter	-0.070	-0.282	-0.092	-0.192
	(0.069)	(0.056)	(0.060)	(0.153)
Biosimilar Approval Counter	0.104	0.111	0.0263	0.139
	(0.049)	(0.036)	(0.048)	(0.077)
Drug FE	x	x	x	x
Year FE	x	x	x	
Age FE				x
N	1,438	1,438	596	1,434
Adjusted R^2	0.989	0.945	0.996	0.929

Notes: Standard errors are clustered at the drug level.

C.3 *Penetration of Biosimilars in Medicare Part B*

In this section, we use Medicare Part B data to examine the penetration of biosimilars on the market. We focus on Medicare Part B for completeness, because SSR Health contains data on only seven of the biosimilars and happens to only track at most one biosimilar per molecule. The results presented in Figure 10 show revenue share of originator biologic and biosimilars, and suggest that most biosimilars have struggled to gain market share. The one exception is filgrastim.

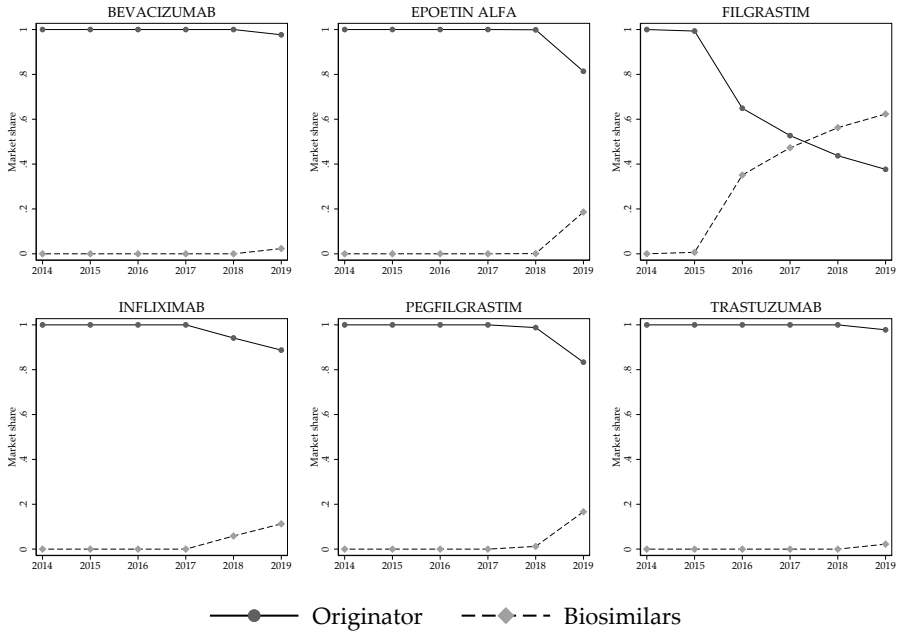


Figure 10: Market penetration for select biosimilars, Medicare Part B