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ABSTRACT

Biologics accounted for roughly $145 billion in spending in 2018 (IQVIA, 2019). They are also the fastest growing segment of the pharmaceutical industry. The Biological Price Competition and Innovation Act (BPCIA) of 2010 created an abbreviated pathway for biosimilar products to promote price competition in the market for biological drugs. There was great anticipation that the BPCIA would lead to a moderation in drug prices driven by market competition. The observed levels of competition and the accompanying savings have not reached those expected levels. we investigate the early impacts of entry of potential biosimilar competitors on use of biosimilars and prices for biological products. We focus especially on entry by biosimilars and how altered market structures stemming from the implementation of the BPCIA are affecting the prices for biological products subject to biosimilar competition. We do so by studying 7 products that have recently faced biosimilar competition. We estimate fixed effects and Instrument Variables models to estimate the impact of market competition on prices. Our results indicate that in the range of 1 to 3 entrants each additional marketed product results in a reduction in weighted average market prices of between 5.4 and 7 percentage points.

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I. Introduction

Biologics accounted for roughly $145 billion in spending in 2018 (IQVIA, 2019). They are also the fastest growing segment of the pharmaceutical industry. The market environment for biological products and competition in that market segment are unique in terms of the regulations governing market entry and competition, payment arrangements by public and private insurers and the intellectual property claims made by manufacturers. Biological products have been largely insulated from price competition. For example, the top 10 biologics each have cumulative sales of more than $40 billion since launch and have been exclusive sellers for an average of 17 years (Aitken, 2020). The last several years have been characterized by a shift towards greater market competition from so-called biosimilars due in part to the continuing development of regulations implementing the Biological Price Competition and Innovation Act (BPCIA) of 2010. IQVIA estimates that about 17% of the biologics market is potentially accessible to biosimilar competition.

The BPCIA created an abbreviated pathway for biosimilar products to promote price competition in the market for biological drugs. There were high expectations for the legislation that would introduce price competition into markets for biological products. The Congressional Budget Office in 2008 estimated that the BPCIA would reduce prescription drug spending by $25 billion over 10 years and federal spending by $5.9 billion. Mulcahy et al (2014) projected savings of $44 billion over the 2014-2024 period. The observed levels of competition and the accompanying savings have not reached those expected levels. The combination of slow regulatory responses by the U.S. Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS), regulatory manipulations by the industry that create barriers to entry, contracting practices between PBMs and manufacturers, physician concerns about the degree of similarity, and uncertainty created by patent litigation have limited the competitive impact of biosimilars (Zhai, Sarpartwari, and Kessleheim, 2020; Wong, Rumore, and Chan, 2017; Falit, Singh, and Brennan 2015). These circumstances have prompted Congress to consider several legislative initiatives that would promote a larger and more dynamic role for biosimilar products in the prescription drug marketplace.

Prior to 2020 there had been 11 biological products for which the FDA has approved at least one biosimilar product. For these 11 drugs there have been 29 biosimilar products approved by the FDA. Of the 11 originators facing potential biosimilar competition there have been 9 drugs subject to competition from a total of 19 biosimilar products. We will focus on 7 of these (non-insulin) products. In this paper, we investigate the early impacts of entry of potential biosimilar competitors on use of biosimilars and prices for biological products. We focus especially on entry by biosimilars and how altered market structures stemming from the implementation of the BPCIA are affecting the prices for biological products subject to biosimilar competition.

II. Background and Context

The Congress sought to inject competition into biological product markets following loss of exclusivity rights that was parallel to the Hatch-Waxman Act of 1984, that applies to so-called “small molecule” products (Congressional Research Services, 2019). That legislation has been widely hailed as a success even if in recent years proposals are being made to modernize the statute. The Hatch-Waxman Act created an abbreviated pathway for small molecule generics to

enter the market. That served to reduce both the regulatory and pecuniary burdens of market entry. The entry by low cost "chemical carbon copies" of brand name drugs following loss of exclusivity resulted in drugs experiencing generic drug competition experiencing shifts of 75% to 90% in the volume of sales to generic products within the first-year post loss of exclusivity or LOE (Frank, McGuire and Nason, 2020). These volume changes were accompanied by reductions in the average price of a molecule facing generic competition of 60% to 90% by the end of the first year following generic entry.

The BPCIA was included as Title VII of the Affordable Care Act of 2010. Like the Hatch-Waxman Act, it created an abbreviated pathway to market for biological products that could show that they were "highly similar" or biosimilar or interchangeable with an existing approved biological product. A drug is to be judged as biosimilar if it is "highly similar to the reference product by extensively analysing (i.e., characterizing) the structure and function of both the reference product and the proposed biosimilar [and] has no clinically meaningful differences from the reference product in terms of safety, purity, and potency."[1]

The FDA has broad discretion in deciding what evidence is sufficient to assess whether a drug is biosimilar. Unlike being an AB rated generic in the small molecule drug context, being found to be biosimilar does not entitle a pharmacist to substitute a biosimilar for the originator unless the prescribing provider endorses such a move. Interchangeable biosimilars are biosimilar drugs that can be shown to produce the same clinical result in a patient as the originator. Interchangeable drugs can be substituted by a pharmacist without prescriber approval.

Policy actions have been relatively weak in promoting price competition in the biologics arena. The FDA only recently issued guidance on standards for interchangeability. They have adopted drug naming conventions that reinforce physician concerns about similarity (FTC, 2018). CMS has adopted policies that insulate originator biological products from direct "head to head" price competition under Part B of Medicare, by allowing each product (originator and individual biosimilar) to carry its own reimbursement code and price (since 2018). This contrasts with the case of small molecule drugs where the branded product and its generics fall into the same payment code that causes intensified price competition. Finally, manufacturers have instituted aggressive contracting and rebate practices aimed at deterring PBMs and insurers from giving beneficial formulary placements to biosimilars. Anti-trust investigations are in relatively early stages in this area.

Europe through the European Union created an abbreviated pathway for biosimilars 5 years earlier than the U.S. In 2020, the EU overall has more originators facing biosimilar competition than in the U.S. (16 vs. 9). In markets with biosimilars those in the EU face a larger number of competitors that claim a larger market share than in the U.S. (Brill and Robinson, 2020, Scott Morton et al, 2018). These larger aggregate results mask a considerable amount of heterogeneity that stems from country specific purchasing and reimbursement policies (IQVIA, 2018).

[1] https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products#biosimilar

III. Economic Framework

During the period that patents and regulatory exclusivities legitimately prevent biosimilar competition, manufacturers of originator biological products typically enjoy sufficient market power to price their products substantially above marginal production costs. Economic research has shown that, when generic manufacturers enter the market, they price their generic products well below the prices of their branded counterparts. As a result, generic manufacturers typically capture a large share of sales, resulting in a reduction in average price paid for a prescription for the molecule (branded plus generics). In many markets, a new generic product quickly faces intense competition from other generic manufacturers, which within a few years drives prices down to a fraction of the branded price at the time of generic launch. A central issue in this research is to what extent do biosimilar markets display similar outcomes to the experience of generic small molecule drugs.

We consider two general types of competition: homogeneous-product competition and differentiated-product competition. *Homogenous-product competition* occurs among identical or nearly identical products. When products do not differ in their attributes (or characteristics), price competition is most intense as price in consumer choice. *Differentiated-product competition* occurs among products that vary, sometimes considerably, in terms of product attributes, consumer choice is therefore based on price but also on how they view each product's combination of attributes. Therefore, competition based on price will be more important among products with relatively similar attributes.

The logic behind the BPCIA is to create a pathway for bringing relatively homogeneous competitive biological products to market at relatively low costs to foster price competition. Thus, the proposition behind the expected savings is that there will be multiple relatively homogeneous competitive products entering markets for biological products that have lost their claims to exclusivity. This entry would in turn result in price competition driving down the price of a treatment below the supra-competitive prices produced by patent monopolies. For generic drugs under the Hatch-Waxman Act, the typical market responses to competitive entry are large shifts of market share to generic products and substantially lower average price of the molecule.

In the small molecule context, branded drug companies respond to generic competition by ending promotion of the brand and either raising prices or leaving them largely unchanged. This is due in significant measure to the poor prospects of holding on to market share because of the ability for substitution at the pharmacy. In the case of biological drug products, the institutional context differs markedly. There are as yet no opportunities for substitution at the pharmacy because the standards for interchangeability have only recently been set forth and no biosimilars have been deemed interchangeable. Thus, makers of biosimilars that are not approved as interchangeable rely heavily on physicians to alter their prescribing habits to generate demand for their products. The regulatory designation of biosimilar but not interchangeable leaves the possibility of meaningful differences between originator and its biosimilars. This differentiation creates friction in demand for biosimilars and means that by reducing price modestly an originator product may retain more market share than would be the case in small molecule markets with generic competition.

The experience in Europe suggests that originator firms may adopt different pricing strategies than is the case with small molecule drugs (IQVIA, 2018). The frictions related to shifting market shares towards biosimilar has some firms in Europe to drop prices for their products in an effort to hold on to market share at somewhat elevated prices. In this analysis, we offer some preliminary evidence of pricing strategies in U.S. markets.

IV. Empirical Implementation

A. Empirical Strategy

We focus on the link between market structure or competitor entry and prices. In the empirical analysis, we estimate the impact of market entry on average prices for a product (originator plus biosimilars) and on originator pricing strategies. Specifically, we estimate the impact of market entry by biosimilars on the ratio of the originator price to the pre-biosimilar entry originator price and the ratio of the average product price to the pre-biosimilar entry originator price. We use the *average sales price* reported by the Medicare program as our measure of price. We also examine movement in originator price in relation to the number of competitors in the market.

A basic challenge to estimation of the impact of changing market structure on prices relates to the potential endogeneity of market structure (Berry, Gaynor, Scott Morton, 2019). To address the potential endogeneity, of market structure, in a model of pricing, we estimate two models where the ratio of average product price to pre-biosimilar entry originator price is a function of the number of biosimilar competitors.

The first model uses a fixed effects approach to estimation where each product group has its own intercept or fixed effect. That assumes that the statistical endogeneity arises from unobserved product specific characteristics that create a correlation between the error term in the model and the market structure measure. The basic model specification is set forth in equation (1).

$$(1)\ ASP\ RATIO = \beta_0 + \beta_1 entered\ biosimilars + time\ trends + drug\ fixed\ effects + \epsilon$$

Because the assumption that the endogeneity originates solely from time invariant unobservable product features is strong, we specify an alternative model that relaxes that restriction. Our second specification allows for other sources of endogeneity by estimating an Instrumental Variables (IV) model. The instrumental variable in this model relies on regulatory decisions to approve one or more biosimilars for marketing. The timing of FDA approval is an exogenous predictor of market entry that is likely uncorrelated with market structure and strongly correlated with the number of products entering a product line. Our exclusion restriction would be invalid if there was evidence that the timing of approval itself is driven by drug specific time variant features that represent strategic considerations about market positioning similar to the entry decision itself. This is unlikely to be the case for two reasons. First, we restrict our measurement approach to applications that are approved so that any withdrawals of applications are automatically precluded. Second, the approved biosimilars products have had to face post-approval litigation, and regulatory hurdles due in part to an evolving regulatory framework at the FDA, and regulatory barriers erected by originator biologic rivals (Johnston, Walter, and Tataru, 2020; Zhai, et al., 2019). Based on our review of the trade literature we propose that the brunt of the delaying tactics is concentrated in the post-approval period, which is the basis for our

concern about the endogeneity of market entry stemming from time varying market conduct. Approval dates, on the other hand, provide an indicator for a credible threat of competition but are not impacted by time varying actions of the originator firms, thus allowing for a valid exclusion restriction.[2]

We estimate the IV model with fixed effects and test for the strength of the proposed instrument. Thus, our focus in estimation is to estimate the coefficient β_1, where we posit a coefficient that is negative in sign.

We also examine originator price response strategy by examining differences in the pattern originator prices and the weighted average product line prices as biosimilar entry take place. We include an analysis of volume share shifts to aid in interpreting the price movements.

B. Data

We assembled data on prices and volumes for the drugs under consideration. Our pricing data is derived from CMS's Average Sales Price (ASP) drug pricing files and our volume data are derived from IQVIA's national sales perspective. We also assembled approval dates for the biologics and biosimilars using information from FDA's purple book. In addition, we compiled market entry dates using IQVIA data and web searches for company press releases. These sources and our process of data curation are described in detail below:

Molecules studied:
As mentioned earlier, there were 11 biologics with approved biosimilars in 2019: Neupogen, Remicade, Epogen, Neulasta, Avastin, Herceptin, Rituxan, Enbrel, Humira, Lantus and Humalog. Lantus and Humalog are insulin products that are predominantly covered by Medicare Part D which is why they are dropped from our analysis. For Enbrel and Humira, while they have a number of biosimilars approved – 2 in the case of Enbrel and 5 in the case of Humira – the biosimilars have not yet entered the market primarily due to patent litigation (Norman, 2016). For this reason, these drugs were also dropped from our sample.

Dates of approval and market entry:
For the 7 biologics and their associated biosimilars that we focus on in this paper, we curate the list of approved biosimilars and their approval dates from FDA's Purple Book online dataset that records application information on biological products including biosimilar and interchangeable products which are approved by the FDA. Approval dates are different from market entry dates with the latter likely being more important for studying price and volume responses, so we assembled a list of market entry dates using press releases from company websites and dates at which IQVIA recorded a transaction for a particular biosimilar (Table 1).

Prices of biologics and biosimilars:

[2] Even in our IV regressions, we do use product-line specific fixed effects thus accounting for the possibility for drug specific factors, such as the size of the market, thatwould result in more approvals in larger markets etc.

We use data from CMS on ASPs of the biologics and biosimilars that we consider. ASPs are reported by CMS for every quarter since the passage of the Medicare Modernization Act of 2003. ASP is calculated using a manufacturer's self-reported sales of a drug to all purchasers in the US in a particular quarter divided by the number of units sold in that quarter. The sales number is "net of any price concessions, such as volume discounts, prompt pay discounts, cash discounts, free goods contingent on purchase requirements, chargebacks, and rebates other than those obtained through the Medicaid drug rebate program"(U.S. Department of Health and Human Services, 2010). Since CMS relies on reporting by individual manufacturers, there is a two-quarter lag between reported ASP and the sales data that it was based on. For this analysis, we adjust for that by mapping ASP data to volume data from two quarters earlier. This allows our data to be mapped exactly to what manufacturers were selling their drug for in that quarter and prevents us from relying on proxies such as wholesale acquisition cost which are used when a new drug is introduced to the market and previous quarter sales data is unavailable.

ASP is calculated at the HCPCS code level and uses a standard dosage amount which implies that sales of the same molecule with different dosages are aggregated together when calculating the ASP. For example, Neupogen is given an HCPCS code "J1442" and has an ASP reported at the 1MCG standard dosage level.

The assignment of HCPCS codes is especially important to mention in the case of biologics and biosimilars since the process differs for the small molecule drugs. The difference between small molecules and biologics arises in the assignment of HCPCS codes. For small molecules, originator molecules and generics share a HCPCS code and thus are reimbursed together. However, for biologics, the originator biologic is assigned a different HCPCS code than the biosimilars and each biosimilar is assigned its own HCPCS code.[3]

Sales volume information:

Our data on pharmaceutical sales from IQVIA is captured from their national sales perspective (NSP) Database. These data are representative of the transactions in the United States, capturing over 95% of all sales for these molecules. Our data extends from the third quarter of 2014 to the first quarter of 2020 with the exception of Neupogen and its biosimilars for which we have data starting in the third quarter of 2013. This is because Neupogen began facing biosimilar competition in the first quarter of 2014, before the other biologics in our sample.

The unit of analysis was the molecule-quarter, for example Filgrastim in 2018 q1. The quantity of sales was measured in terms of the Extended Units which measure product volume in terms of

[3] While regulation changes suggest that originally all biosimilars were assigned the same HCPCS code which meant that the second biosimilar would be reimbursed at the rate of the biosimilar currently in the market for its first two quarter instead of the wholesale acquisition cost and this was changed in 2018 when each biosimilar was also assigned its own HCPCS code, we find mixed evidence for that in our particular dataset. For example, the only cases this would impact are Neupogen and Remicade since they have biosimilars entering the market before 2018. We see that Granix (J1447) and Zarxio (Q5101) are both assigned different HCPCS codes even before 2018. Renflexis and Inflectra are assigned the same HCPCS code (Q5102) but they only share it for one quarter since Renflexis appears on the market in the last quarter of 2017.

pills or millilitres. For non-oral products such as injectables the definition is in terms of mls for a wet formulation or a unit of 1 for a dry vial. In our case, Trastuzumab is available as a vial in two different dosages whereas Infliximab is available as a vial in one dosage only. The remaining are all injectables measured in milliliters . The NSP records sales volume information on the product-form (e.g. oral solid or injectable), strength (e.g. 10 milligram or 10 milliliters), and the distribution channel (e.g. retail or mail order) level. After standardizing units to map to units used in the CMS HCPCS standard dosage calculations, we aggregated these to the combined molecule-product quarter level.

Table 1 Drugs Studied and Biosimilar Entry

Biologic	Baseline Sales[4] prior to first biosimilar entry ($ millions)	Number of biosimilars in market (as of March 2020)	Number of biosimilars approved (as of March 2020)
Avastin*	822	2	2
Epogen	609	1	1
Herceptin*	777	4	5
Neulasta*	1054	3	3
Neupogen	235	3	3
Remicade	1344	2	4
Rituxan*	1072	2	2

The final data for our analysis consists of 165 observations at the molecule-quarter level (28 observations for Neupogen, 22 observations for Epogen and 23 observations for the remaining molecules). There is substantial variation in how long each biologic is exposed to biosimilar competition in our data and consequently, variation in how long we observe a biosimilar for.

V. Results

As noted earlier, our primary focus is on how average molecule (or market) prices and originator prices move in response to biosimilar competition. We report simple statistics and graphical representations of price movements associated with a changing competitive environment for some biological products. Table 2 presents the pre-biosimilar entry price of the product, the average product (molecule) price 2 quarters post biosimilar entry and the post entry originator price. There is considerable variation in the price reductions that take place following biosimilar entry. The observed range of price declines goes from 1% for Rituxan to 18.8% for Neulasta. Some of that variability is because some of the drugs studied were only observed for one quarter post biosimilar entry. We also hypothesize that some of the observed variation stems from the amount of biosimilar entry and the intensity of competition.

[4] Here, sales value is sales value as recorded in IQVIA data which is indicative of wholesale prices.

Table 2 also highlights considerable variation in the post-biosimilar entry market shares held by the originator manufacturer. The originator market shares range from a high of 95% for Remicade to a low of 33% for Neupogen, with most falling in the 72% to 93% interval. The observed variation may stem from the duration of time that an originator has faced biosimilar competition, the pricing and marketing strategy of the originator or other market frictions such as perceived degree of bio-similarity.

Table 2 Pre-Post Biosimilar Entry Prices

Biologic	Average molecule price pre-entry	Average molecule price post-entry**	Price of originator post-entry**	Originator share of sales post-entry**
Avastin*	191.5	175.8	184.9	.76
Epogen	23.2	20.6	20.8	.92
Herceptin*	1508.8	1381.0	1448.0	.77
Neulasta*	7370.6	5898.5	5986.3	.72
Neupogen	543.4	396.1	545.7	.33
Remicade	775.6	735.8	743.7	.95
Rituxan*	89.07	86.5	88.1	.93

*These biologics had biosimilar entry in 2020q1 which is the last period of our data.
** Post entry is defined as two quarters after last biosimilar entry except in the cases of biologics marked with a * which had biosimilar entry in 2020q1 the last period for our data.

A. Fixed Effects Models

We present estimates for three specifications of the fixed effects model set out in equation (1). Each has the ratio of the average product line (originator and biosimilars) price to the originator price two quarters pre-biosimilar entry on the left-hand side of the model.

The three specifications involve a) product-line specific fixed effects with no time trend control; b) product line fixed effects with a quadratic time trend; and c) product line and quarter (time) fixed effects. Each model includes the number of biosimilar entrants as a regressor. It is the coefficient estimate for that variable that is of interest here. The results for those models are reported in Table 3.

Table 3a: Fixed Effects Models – Weighted ASP ratio

VARIABLES	(1) Weighted ASP	(2) Weighted ASP	(3) Weighted ASP
Biosimilars in market	-0.0615***	-0.103***	-0.0942***
	(0.0112)	(0.0139)	(0.0185)
Constant	0.915***	0.825***	0.903***
	(0.0206)	(0.0252)	(0.0469)
Observations	165	165	165
R-squared	0.317	0.454	0.508
Drug fixed effects	YES	YES	YES
Quadratic time trends	NO	YES	NO
Quarter fixed effects	NO	NO	YES

Robust standard errors in parentheses

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

The estimated coefficient for the number of biosimilars that entered the market were all negative and quite precisely estimated indicating that they were significantly different from zero at the 99% confidence level. The model with no time controls indicates that for each additional entrant there is a 6.1 percentage point decline in the average price to pre-biosimilar originator price expressed as a percentage (hereafter the price ratio). The two models that include controls for time both estimate the impact of additional generic competitors to result in a 9.3-10.3 percentage point decline in the price ratio for each additional biosimilar competitor. The addition of the time controls affects both the point estimate for the number of biosimilar competitors and the overall fit of the model. The explained variance nearly doubles with the inclusion of the time controls.

Table 3b: Fixed Effects Models – Originator ASP ratio

VARIABLES	(1) Originator ASP	(2) Originator ASP	(3) Originator ASP
Biosimilars in market	-0.0221**	-0.0706***	-0.0743***
	(0.00974)	(0.0104)	(0.0143)
Constant	0.899***	0.779***	0.772***
	(0.0187)	(0.0171)	(0.0302)
Observations	165	165	165
R-squared	0.243	0.526	0.565
Drug fixed effects	YES	YES	YES
Quadratic time trends	NO	YES	NO
Quarter fixed effects	NO	NO	YES

Robust standard errors in parentheses

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

Table 3b shows the impact on originator price with prices declining by roughly ~7 percentage points in our preferred specifications, which control for time trends. This decline is slightly smaller than what is observed for the average molecule price which also takes into account sales that accrue to the lower priced biosimilars.

B IV Models

In this section, we report results for IV models. As described earlier, our identification strategy relies on using the timing of FDA approval of biosimilars as the exogenous instrument. Overall, there are more approvals than actual entrants. Thus, the instrument is correlated with the outcome but does not measure the same behavior. It relies on a scientific and political process largely apart from market considerations. As in the case of the fixed effects model we estimate three specific specifications for both the average product line price ratio and the originator price ratio. We report first stage results and reduced form price ratio results in the appendix. We conducted weak instrument tests for all the IV models estimated. In all cases we reject the hypothesis that the instrument is weak with F-Tests ranging from 28 to 100 across the specifications (for first stage results and reduced form estimates see the Appendix A).

Table 4a report IV estimates for the ratio of average product line prices to the pre-biosimilar entry originator price. We include the same three general specifications as in the previous models. The IV results for the predicted number of biosimilar market entrants show that the coefficient estimates for all three models are negative and significantly different from zero at the 0.1 level. The estimated coefficients indicate that the product line average price ratio expressed in percentage terms declines by between 4.5 and 7.7 percentage points for each biosimilar entrant. It is important to note that the maximum number of biosimilar entrants observed in our data is 3.

Table 4a: Instrumental Variables Analysis with Weighted ASP as the outcome

VARIABLES	(1) Weighted ASP	(2) Weighted ASP	(3) Weighted ASP
Biosimilars in market	-0.0457***	-0.0773***	-0.0566*
	(0.0139)	(0.0247)	(0.0294)
Constant	0.907***	0.828***	0.900***
	(0.0196)	(0.0238)	(0.0814)
Observations	165	165	165
R-squared	0.306	0.439	0.484
Drug fixed effects	YES	YES	YES
Quadratic time trends	NO	YES	NO
Quarter fixed effects	NO	NO	YES

Robust standard errors in parentheses

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

Table 4b reports model estimates for three specification of IV models with the ratio of originator prices to pre-biosimilar entry originator prices. The coefficient estimates on the number of biosimilar entrants are all negative. The specification without time controls (column 1) estimated a coefficient for the expected number of biosimilars that was negative in sign but imprecisely estimated and not significantly different from zero at conventional levels of significance. When time controls are added (columns 2 and 3), the coefficient remain negative grow in magnitude and are precisely estimate and are significantly different from zero at the 99% confidence level. The model with the quadratic time trend yielded an estimate for the number of biosimilars indicating a 6.3 percentage point reduction in the originator price ratio for each new biosimilar added to the market. The model using fixed time effects obtained an estimate showing a 5.4 percentage point reduction in the originator price ratio.

Table 4b: Instrumental Variables Analysis with Originator ASP as the outcome

	(1)	(2)	(3)
VARIABLES	Originator ASP	Originator ASP	Originator ASP
Biosimilars in market	-0.0125	-0.0639***	-0.0549**
	(0.0133)	(0.0225)	(0.0262)
Constant	0.894***	0.780***	0.942***
	(0.0184)	(0.0165)	(0.0720)
Observations	165	165	165
R-squared	0.237	0.525	0.557
Drug fixed effects	YES	YES	YES
Quadratic time trends	NO	YES	NO
Quarter fixed effects	NO	NO	YES

Robust standard errors in parentheses

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

C. Examining Originator Pricing Strategy

A second question we sought to shed light upon involves the volume response to biosimilar entry and the pricing strategy adopted by originator firms. As Figure 1 shows, there is significant variation in how much and how quickly, the originator loses market share once a biosimilar enters the market. For example, in the case of Remicade, only about 3% of the originator's market is lost, 1 year after the biosimilar entered. Conversely, Neulasta has lost 20% of its market share and Neupogen 16% of the market share 4 quarters after biosimilar entry.

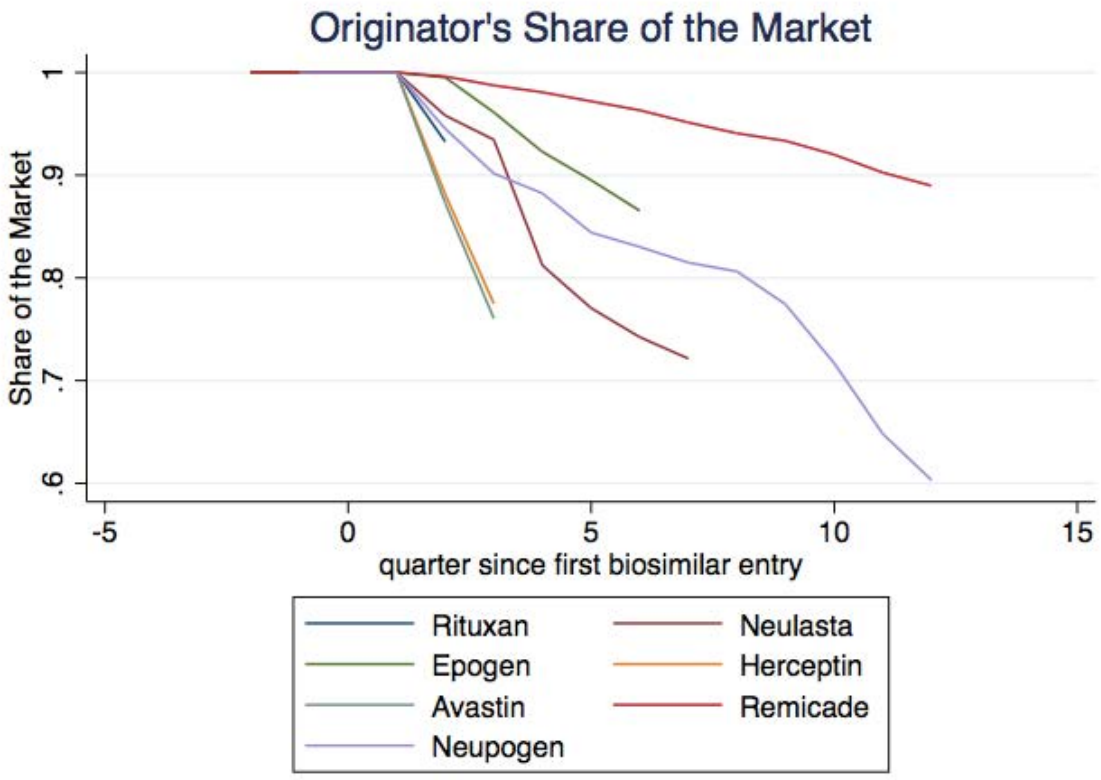

Figure 1: Originator's share of the market following biosimilar entry

Since the share that is captured by the biosimilar may depend on how the originators change their prices after biosimilar entry, we examined the degree to which the weighted average prices over time as a ratio of pre-entry originator price track the originators price. We offer some descriptive evidence on this issue. We do so by comparing the movement of originator prices and the weighted average price for the product line. The closer these two curves are to one another following biosimilar entry the greater is the influence of originator price reduction. In contrast, if the spread between the curves for weighted average product line price and the originator price grows with biosimilar entry this suggests a pattern more like what has been observed with small molecules and the response by branded products to generic competition. We posit that by dropping its price in response to biosimilar entry an originator product may be able to maintain considerable market share. In examining the patterns of prices for the 7 product lines examined we noticed two dominant patterns of price behavior by the originators. To highlight these results, we illustrate with two cases below (we include the additional drugs weighted average graphs as Appendix B). The two product lines presented are that of Remicade and its biosimilars, and

Neupogen and its biosimilars. These cases were selected as focal points for two reasons. First, the exhibit very different prices responses by the originator and second because the competitive conditions as measured by the number of biosimilar approvals was similar since both experienced multiple entrants that had time to affect prices. Neupogen had three entrants and Remicade had two during the period that we observe them. For other drugs in our sample which are observed for longer periods of time -- Neulasta, and Epogen – their behaviour appears similar to Remicade.

Figure 2a shows the price movements for Remicade and its biosimilars. The figure shows that the price for Remicade (originator) did not begin to decline until the second biosimilar entered the market. The first biosimilar, Inflectra entered the market at a price that was about 6% below that of Remicade. The second entrant, Renflexis, entered at a price that was nearly 15% below the pre-biosimilar price for Remicade. The prices are all competing drugs continued to drop following entry by Ixifi, reaching prices that were 40% to 50% below the pre-biosimilar entry price for Remicade. It is notable that the price of Remicade dropped by roughly the same amount as that of the biosimilars.

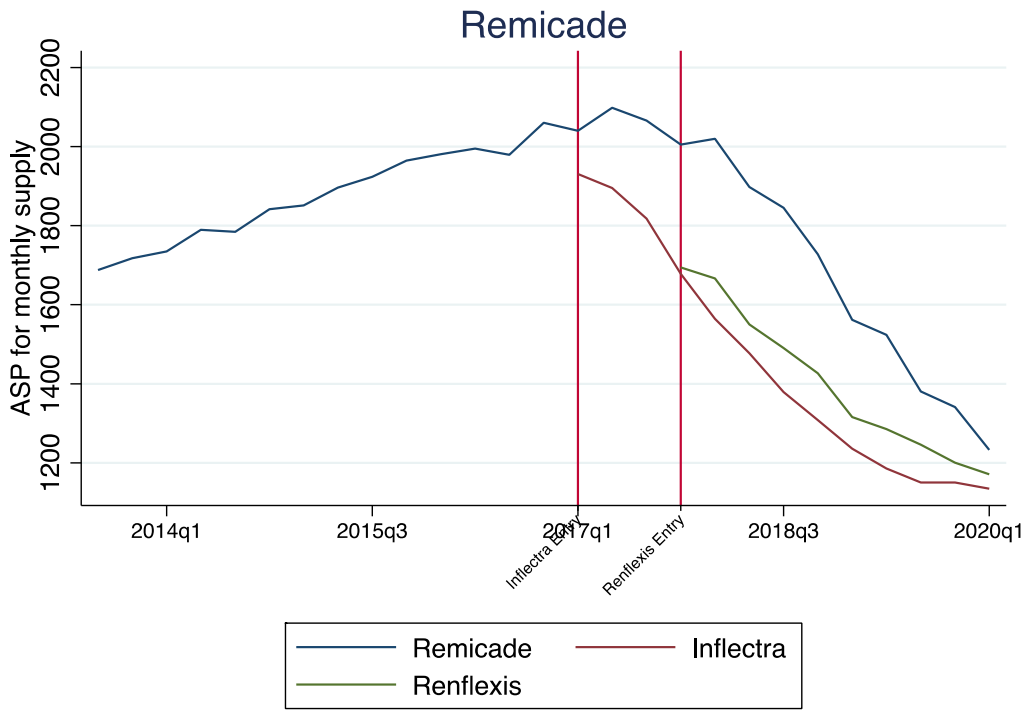

Figure 2a: Monthly prices for Remicade and its Biosimilars. Remicade is used for several different conditions (ankylosing spondylitis, Crohn disease, plaque psoriasis, psoriatic arthritis, pustular psoriasis, RA, and ulcerative colitis) and the typical dosing regimen for most of these regimens is 5 mg/kg at 0, 2, and 6 weeks followed by 5 mg/kg every 8 weeks thereafter. We assume a 70 kg-person for whom number of doses in a year would then equal 8.75 (since one would receive 3 doses in the first 6 weeks and then 5.75 doses in the remaining 46 weeks). At 5 mg/kg for a 70 kg person, that would equal 350 mg per dose or 3,062.5 mg per year or 255.2 mg per month.

Figure 2b presents the patterns of prices for the originator and for the weighted average price of the entire product line. The fact that the two curves track each other so closely suggest that Remicade both dropped its prices and retained a sizable share of the market. This is in marked contrast to what has been observed in branded products following generic entry.

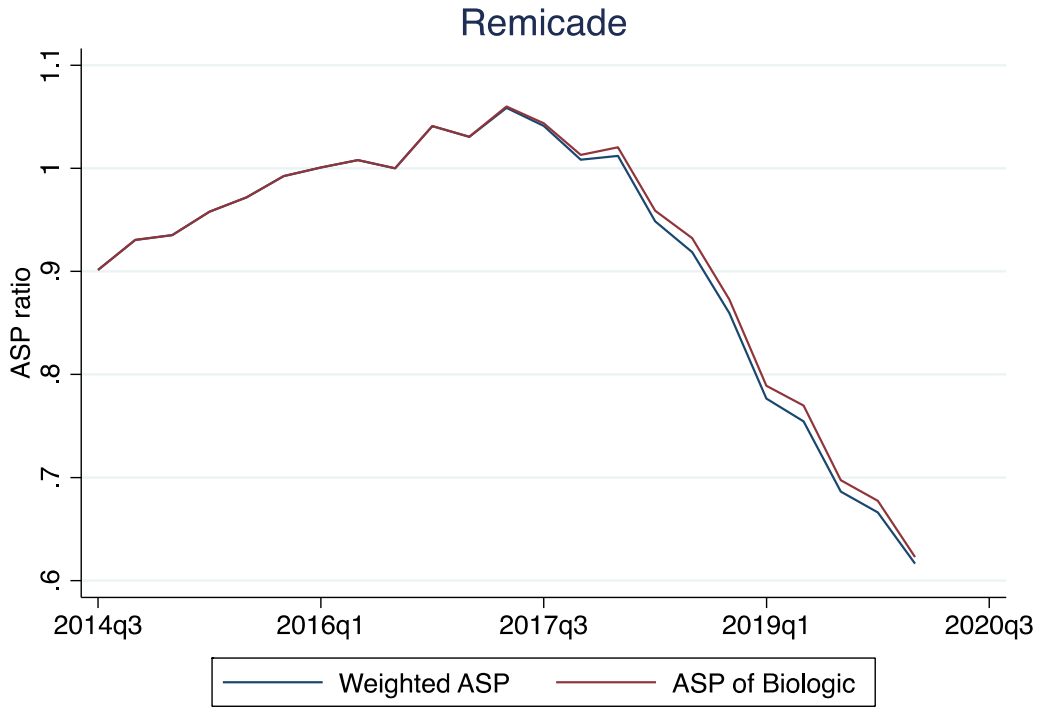

Figure 2b: Remicade price and weighted average of product line

The second case we highlight is that of Neupogen. Figure 3a shows that the price of Neupogen remain quite constant until the third biosimilar entered the market. At that point Neupogen's price fell by about 3%-4%. This modest price decline took place despite the biosimilars offering prices that were 16% to 48% below the Neupogen price. The result was that Neupogen lost over half its sales volume. This is reflected in Figure 3b. We note that our results for Neupogen are quite different from those reported in a recent study (San-Juan-Rodrigez, et al., 2019) that found a substantial drop in net prices of Neupogen following biosimilar entry. The variation in results is likely due to differences in our price data. San-Juan-Rodriguez et al. (2019) use data from SSR health, which estimates average net prices from SEC filings, data on units sold and list prices using a proprietary algorithm. One reason for deviation may be that the net prices include Medicaid and 340-B hospitals whereas ASP explicitly does not include those rates in its calculation. Another reason could be noise in data collected from financial statements. While informative and increasingly in use, the SSR data has not been extensively validated or its reliability tested. Moreover, because ASP is measure of market prices used as a basis for Medicare Part B reimbursement it is important from a policy perspective to understand the impacts of competition on that measure of market prices. For those reasons we focus solely on the ASP measure of prices recognizing the difference in the SSR price for Neupogen.

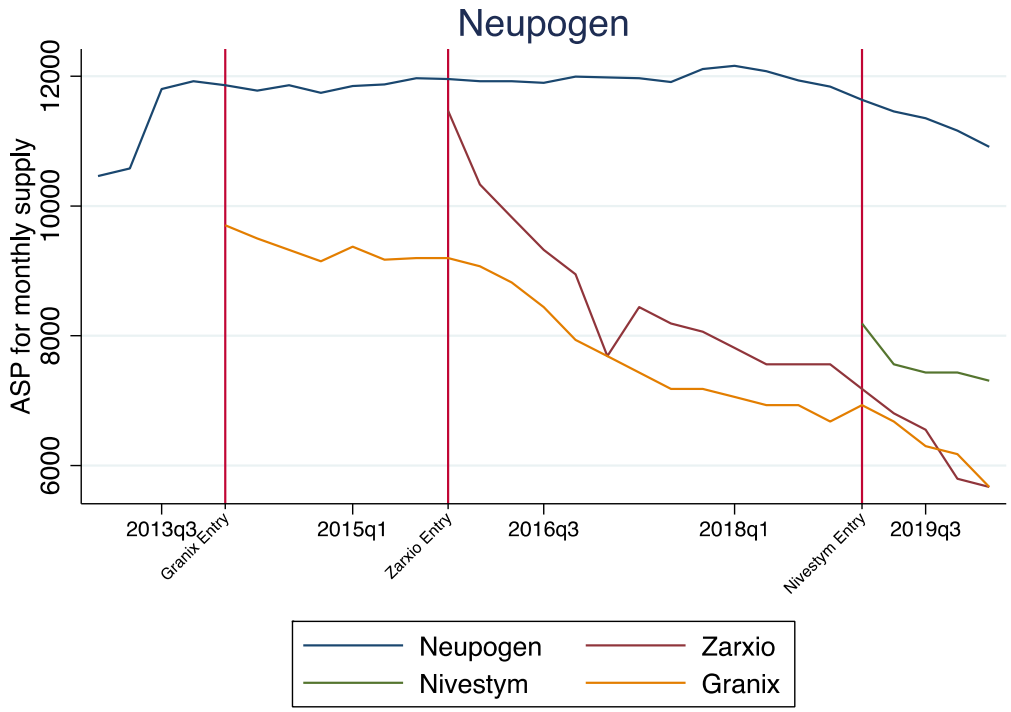

Figure 3a: Prices for Neupogen and its biosimilars. While Neupogen has a number of indications and different dosages are used for different indications and depend on patient reaction, we assume a 6MCG/kg/day dosage for a 70 kg individual for 30 days.

Figure 3b shows strong divergence between the price of Neupogen overtime and the weighted average price of the product line. In this case the significant average price reduction for the product line was largely the product of shift in volume away from Neupogen and towards the biosimilars.

These two cases illustrate two basic pricing strategies adopted by originator firms. While further investigation of these strategies is needed, the other drugs examined in this study display a pattern closer to the Remicade price response. The full set of graphs are presented in Appendix B.

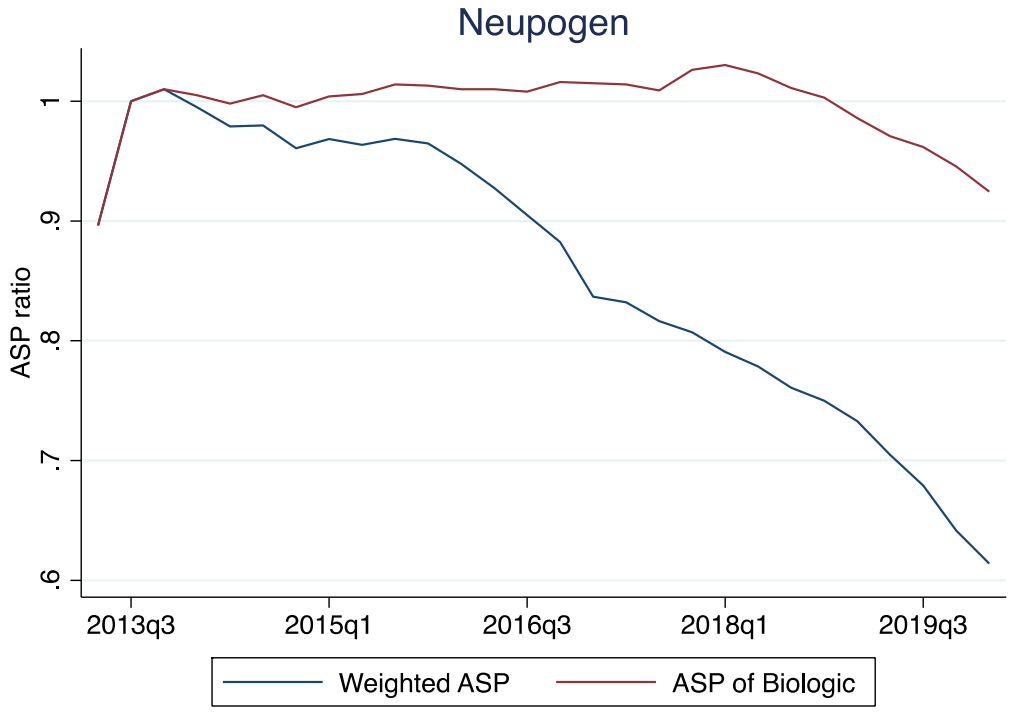

Figure 3b: Neupogen price and weighted average of product line

VI. Discussion

There has been considerable anticipation about the impacts that biosimilar competition would have on markets for biological drugs. Economists have generally agreed that the impacts on prices for biological products would be muted relative to what has been observed when generic drugs compete in small molecule markets (Grabowski, Guha, Salgado, 2014). This is in part because the regulatory framework set out in the BPCIA differs markedly from that of the Hatch-Waxman Act. The inability for the time being for pharmacists to automatically substitute biosimilars for the branded drug, the perception that similarity meaning that there are meaningful differences in products, the fact that many biologicals are physician administered and are often operating under payment regulations that do not foster price competition are among the factors yielding the expectation of smaller savings from competition.

Nevertheless, our results do show that although weaker than in small molecule markets, competitive forces yield important price reductions as the number of competitors increase. Our estimates indicate that weighted average price ratios post biosimilar entry fall by an average of between 4 and 10 percentage points per biosimilar entrant. Our results also highlight that the competitive responses behind these price reductions are heterogeneous and at times quite different from what has been found in small molecule markets. In particular, it is almost universally the case that branded drugs facing generic competition do not reduce their prices and lose between 70% and 90% of their sales in the first-year post-loss of market exclusivity. In the

biologic context, this initial study of the emerging markets led us to observe two basic patterns of competitive response. In both cases, prices fall notably as competition intensifies. In the first, the originator drops its price as multiple biosimilars enter the market. These originators retain a large share of the market. In the second case, the originator does not grant significant price reductions and lower prices are achieved by relatively large volume shifts away from the originator to the biosimilars. While it is premature to draw strong conclusions, it is notable that these two patterns of behavior may have very different long-term market consequences. In one case biosimilars may fail to establish a strong foothold leaving open the possibility of the originator being able to exercise market power in the future if biosimilar entrants do not find the market profitable. In the market with large shifts in market share towards the biosimilars, one might have greater confidence in durability of biosimilar competition. The dynamics are worthy of close monitoring by policy makers and anti-trust authorities.

The fact that a number of biosimilars are approved and do not enter the market, alongside the muted price responses highlight the frictions affecting the development of competitive markets for biological products after loss of market exclusivity. The current difficulty in achieving interchangeability status, the payment structure in Part B of the Medicare program, and the aggressive industry actions with respects to patenting, and insurance contracts all contribute to sluggishness in the evolution of biosimilar competition. Some of these sources of market frictions point to policy measures that may facilitate more robust competition. Altering payment coding so that head-to-head competition is promoted, changing policy towards market exclusivity to reduce the effects of construction of patent thickets and anti-trust enforcement of contracts that deter competition all be profitably explored.

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Appendix A

First stage:

VARIABLES	(1) in_market_biosimilars	(2) in_market_biosimilars	(3) in_market_biosimilars
Approved biosimilars	0.618***	0.547***	0.493***
	(0.0617)	(0.0826)	(0.0926)
Constant	0.236**	-0.0498	-0.265*
	(0.0931)	(0.141)	(0.138)
Observations	165	165	165
R-squared	0.818	0.831	0.872
Drug fixed effects	YES	YES	YES
Quadratic time trends	NO	YES	NO
Quarter fixed effects	NO	NO	YES
F-stat	100.458	43.836	28.384

Robust standard errors in parentheses

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

Reduced form: Weighted ASP

VARIABLES	(1) Weighted ASP	(2) Weighted ASP	(3) Weighted ASP
Approved biosimilars	-0.0282***	-0.0423**	-0.0279
	(0.0103)	(0.0178)	(0.0197)
Constant	0.897***	0.832***	1.012***
	(0.0179)	(0.0252)	(0.0337)
Observations	165	165	165
R-squared	0.209	0.266	0.379
Drug fixed effects	YES	YES	YES
Quadratic time trends	NO	YES	NO
Quarter fixed effects	NO	NO	YES

Robust standard errors in parentheses

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

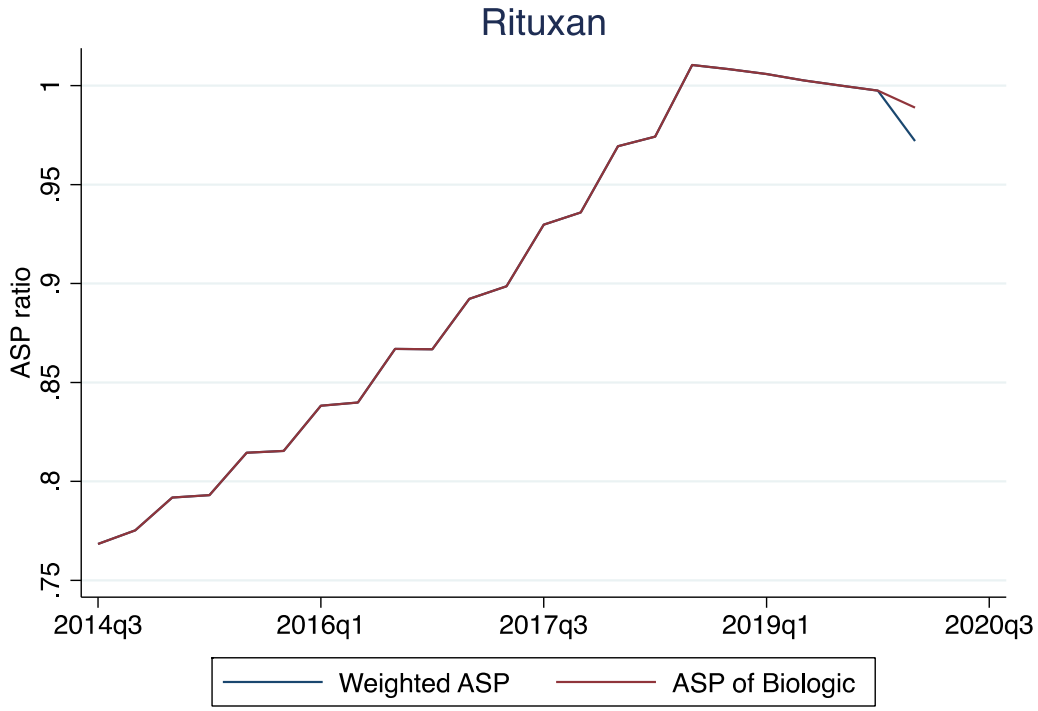
Reduced form: Originator ASP

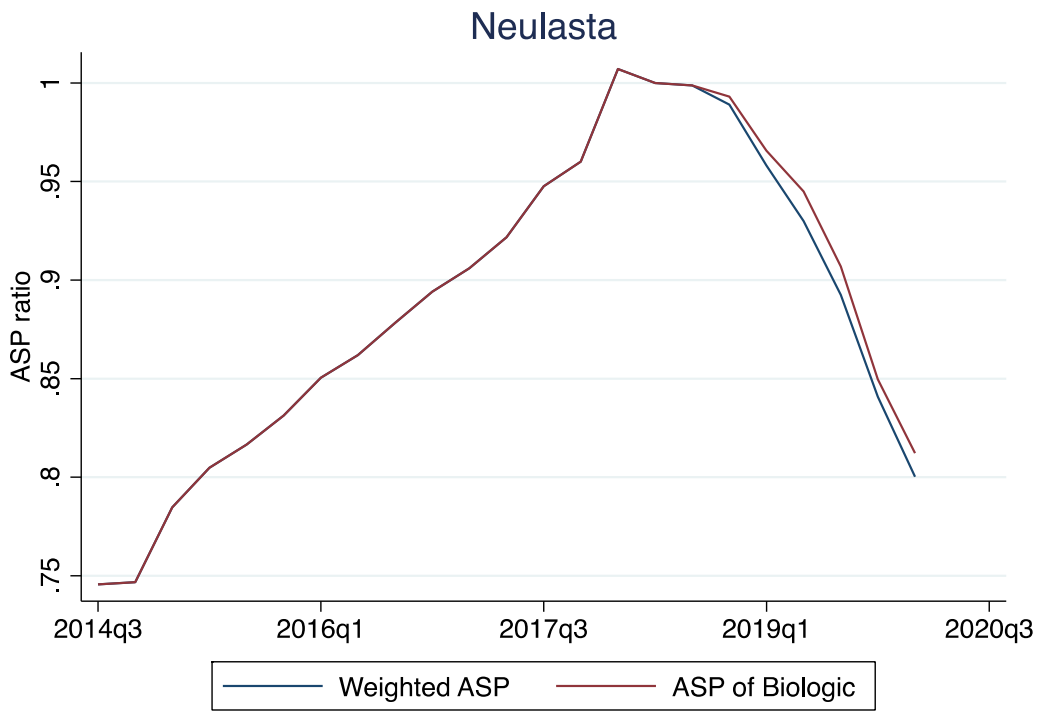
VARIABLES	(1) Originator ASP	(2) Originator ASP	(3) Originator ASP
Approved biosimilars	-0.00774	-0.0350**	-0.0271
	(0.00873)	(0.0158)	(0.0178)
Constant	0.891***	0.783***	0.870***
	(0.0176)	(0.0161)	(0.0171)
Observations	165	165	165
R-squared	0.221	0.427	0.471
Drug fixed effects	YES	YES	YES
Quadratic time trends	NO	YES	NO
Quarter fixed effects	NO	NO	YES

Robust standard errors in parentheses

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

Appendix B:




Neulasta
ASP ratio
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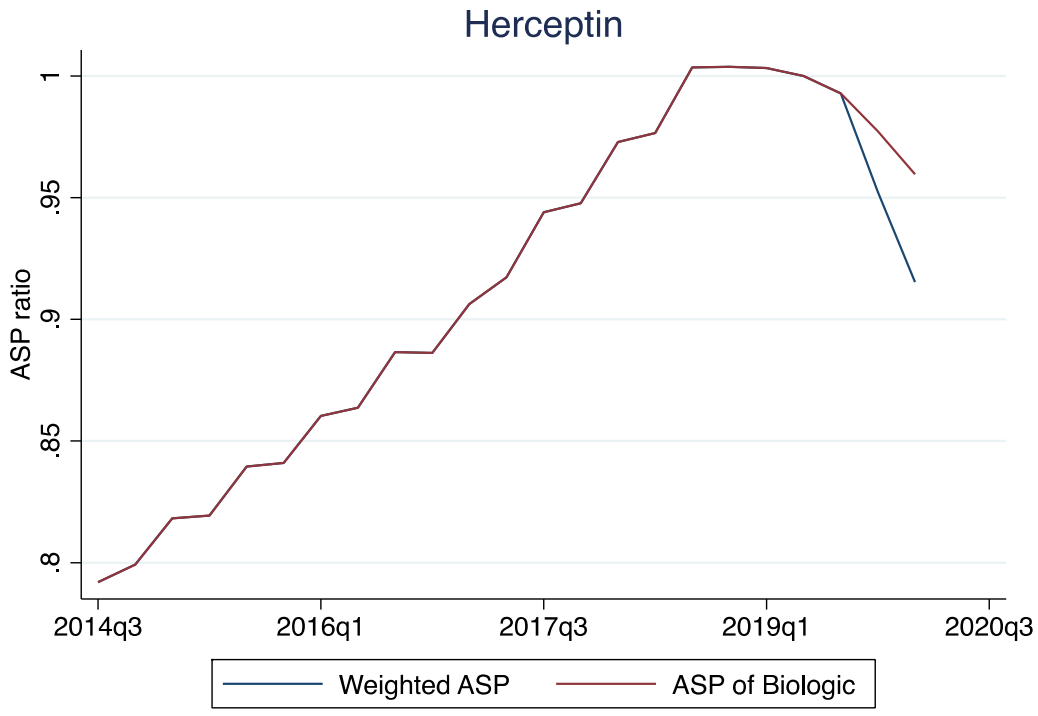
.8
.85
.9
.95
1
2014q3
2016q1
2017q3
2019q1
2020q3
Weighted ASP
ASP of Biologic


Herceptin
ASP ratio
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.85
.9
.95
1
2014q3
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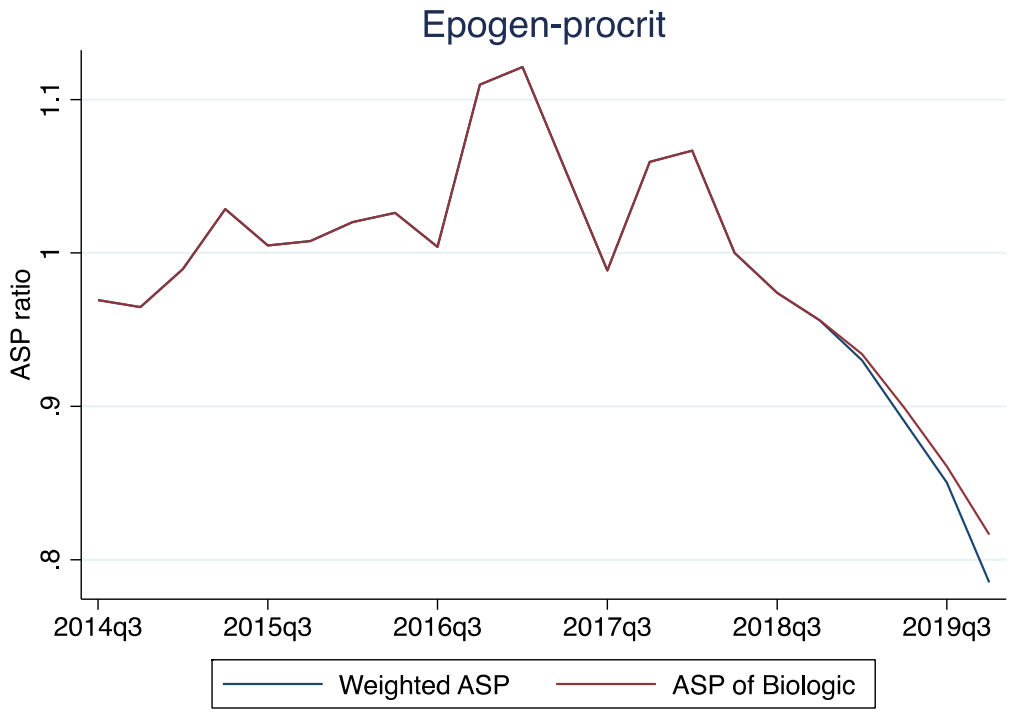
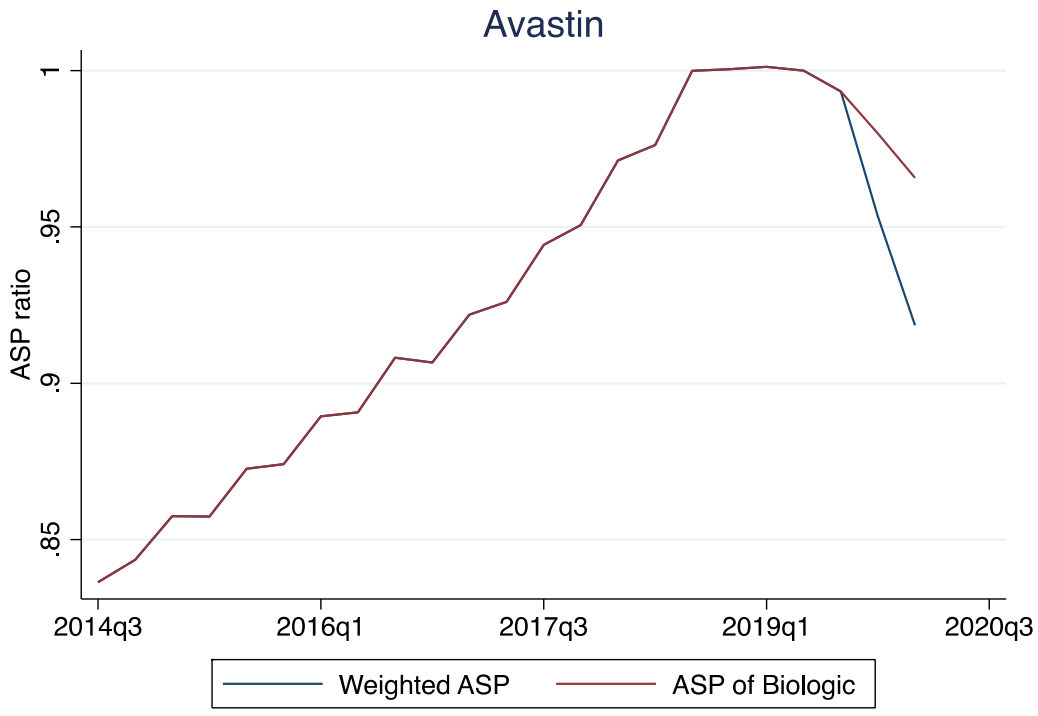
2017q3
2019q1
2020q3
Weighted ASP
ASP of Biologic


Epogen-procrit
ASP ratio
.8
.9
1
1.1
2014q3
2015q3
2016q3
2017q3
2018q3
2019q3
Weighted ASP
ASP of Biologic


Avastin
ASP ratio
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2014q3
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Weighted ASP
ASP of Biologic