Biosimilar Turf Wars

Toulouse Health Economics Conference

June 2025

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Why The U.S. Remains The World's Most Expensive Market For 'Biologic' Drugs

Biologic drugs, made from living organisms, are big moneymakers partly because they have little competition from "biosimilars." It's a very different story in Europe.

By Sarah Jane Tribble
DECEMBER 20, 2018

REPUBLISH THIS STORY

0.4-2% of prescriptions, 40-46% of drug spending

High Expectations for Biosimilars

RAND CORPORATION

Perspective

Expert insights on a timely policy issue

The Cost Savings Potential of Biosimilar Drugs in the United States

Andrew W. Mulcahy, Zachary Predmore, and Soeren Mattke

The U.S. Food and Drug Administration (FDA) is expected to release final regulations outlining lower-cost approval pathway requirements for so-called biosimilar drugs. The introduction of biosimilars is expected to reduce prices, albeit to a lesser degree than small-molecule generics. This Perspective combines prior research and recent data to estimate cost savings in the U.S. market. We predict that biosimilars will lead to a $44.2 billion reduction in direct spending on biologic drugs from 2014 to 2024, or about 4 percent of total biologic spending over the same period, with a range of $13 billion to $66 billion. While our estimate uses recent data and transparent assumptions, we caution that actual savings will hinge on the specifics of the final FDA regulations and on the level of competition.

Context and Motivation

Biologics are complex, protein-based drugs including insulin, monoclonal antibodies to block inflammation in rheumatoid arthritis, and a range of drugs to treat cancer, multiple sclerosis, and other serious diseases. While biologics have revolutionized treatment for many conditions, they are often expensive in terms of cost per dose. Insurers are concerned about rising prices, acceleration in new approvals, and burgeoning pipelines for biologics compared with flat growth and few new nonbiologic "small molecule" drugs. In 2011, eight of the top 20 drugs in the United States in terms of sales were biologics, and year-on-year biologic spending grew at 6.5 percent, compared with 2.3 percent for small molecule drugs.[1] The American Society of Clinical Oncology is calling for value-focused moderation in the use of specialty drugs, many of which are biologics.[2] And patients—who are often asked to bear a share of the cost of expensive specialty drugs through cost sharing—

Disappointingly slow market penetration

Abstract

Biologics are among the most expensive prescription drugs in the United States, posing significant barriers to patient access to necessary treatments. An abbreviated approval pathway for biosimilars, near-identical versions of biologics made by different manufacturers, was created by Congress in 2010 to stimulate competition in hopes of driving down costs and expanding access. However, as of February 2019, only 17 biosimilars have been approved, with only 7 currently on the market. Of the few biosimilars currently available to patients, overall utilization has been limited. This article examines the current landscape of the biosimilar market, characterizes tactics employed by biologics manufacturers to delay market entry and deter prescribing of biosimilars, and assesses ethical issues related to increasing the adoption of biosimilars.

Generics vs Biosimilars: structural market differences

1. **Commercialization channels:**
   - **Generics:** mostly distributed via pharmacies (oral pills)
   - **Biosimilars:** mostly administered within clinics (injectables)

2. **Firm size/scope:**
   - **Generic makers:** atomized fringe
   - **Biosimilar makers:** *large,* ***multi-product firms***

Multi-product facet gives makers *commercial leverage* over clinics

Does commercial leverage shape biosimilar penetration?

Reference Infliximab (J&J)

DARZALEX (daratumumab) injection for intravenous infusion 100 mg/5 mL, 400 mg/20 mL

Balversa® (erdafitinib) 3, 4, 5 mg tablets

CAPLYTA

INVEGA TRINZA™ paliperidone palmitate 273 mg, 410 mg, 546 mg, 819 mg

PREZISTA™ (darunavir)

INTELENCE® etravirine

TECVAYLI® (teclistamab-cqyv) Injection for subcutaneous use 10 mg/mL and 90 mg/mL

Biosimilar Infliximab (Pfizer)

ZAVICEFTA® ceftazidime / avibactam

panzyga® Immune Globulin Intravenous (Human) - ifas 10% Liquid Preparation

Trazimera® trastuzumab

INJECTION Nivestym® filgrastim-aafi

Zirabev® bevacizumab

ZITHROMAX®

Do J&J and Pfizer leverage the rest of their drug portfolios to advance their goals in the infliximab market?

Reference

(J&J)

Table 1: Motivating example: commercial leverage and Infliximab utilization.

(a) Non-Infliximab ("adjacent") drugs

	Spending			
Clinic	J&J	Pfizer	Others	Total
A	$381,998	$27,572	$800,238	$1,209,809
B	$146,770	$473,447	$619,304	$1,239,521
C	$103,809	$97,942	$1,027,996	$1,229,747

	Leverage	
A	0.32	0.02
B	0.12	0.38
C	0.08	0.08

(b) Infliximab

	Number of Claims	
A	29	0
B	0	17
C	30	27

Notes. Clinic C: Alan J. Kivitz MD, PA; clinic B: Houston Rheumatology Institute, TX; clinic A: Nasseri Clinic of Arthritic Rheumatoid Diseases, MD.

Biosimilar

(Pfizer)

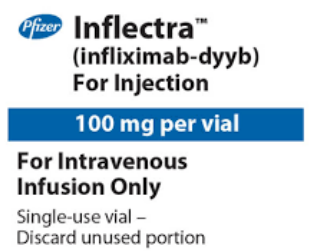
Clinic A:

- 32% of non-infliximab drug purchases from J&J
- J&J lev >> Pfizer's lev
- **Exclusive** assortment (J&J)

Reference

(J&J)

Biosimilar



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Clinic B:

- Pfizer lev >> J&J lev
- **Exclusive** assortment (Pfizer)

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Reference

(J&J)

Biosimilar

(Pfizer)

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Clinic C:

- Pfizer lev = J&J lev
- **Non-exclusive** assortment

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Evidence from 7 Molecule Markets, 2015-2021

- CMS data (20% representative sample)
  - No private insurers, PBMs → focus on vertical maker/clinic relationship
  - Leverage calculated from invoice (ASP) prices

- **Exclusion prevails:** 4/5 clinics administer either the reference or the biosimilar products, not both

- Conjectured mech.: **foreclosure (exclusivity) - inducing rebate contracts**

- Shift-share IV based on clinics' differential exposure to makers' time-varying portfolio strength

Leverage Asymmetry Drives Exclusive Assortment

- **Suggests widespread use of exclusivity-inducing rebate contracts**
  - Asymmetric leverage → **Exclusive** (highest-leveraged maker)
  - Symmetric leverage → **Non-exclusive** (stalemate)
  - Leverage effects → **-11% to +5% of biosimilar share**

- **Biosimilar makers have strong leverage and use it, but face head winds**
  - Biosimilar adoption implies switching costs (training, logistics)
    - Biosimilars are rarely selected under exclusive assortment
  - No leverage effects → +4% biosimilar share

Sugartown Pediatrics v. Merck (2018)

- Incumbent Product: Merck's RotaTeq (pediatric rotavirus vaccine)
- Entrant: GSK's Rotarix
- **Merck's contract:**
  - Portfolio-wide loyalty rebate: 5–7% discount
  - Clinic must purchase minimum 90–95% of rotavirus vaccines from Merck

Leverage → Loyalty Rebates → Foreclosure Risk

- **J&J's Foreclosure-Inducing Rebate** (Pfizer):
  - = $27,572
  - = 6% discount on J&J's adjacent sales
  - Expressed through leverages:

(a) Non-Infliximab ("adjacent") drugs

	Spending			
Clinic	J&J	Pfizer	Others	Total
A	$381,998	$27,572	$800,238	$1,209,809

	Leverage	
A	0.32	0.02

$$\text{FIR}_i^j = \frac{\text{Leverage}_i^{j'} \cdot \text{Total Adjacent Purchases}_i}{\text{Leverage}_i^{j} \cdot \text{Total Adjacent Purchases}_i} = \frac{\text{Leverage}_i^{j'}}{\text{Leverage}_i^{j}} = \frac{0.02}{0.32} = 0.06$$

- **Foreclosure more likely the smaller min(FIR)**

$$\min\{\text{FIR}_i^j, \text{FIR}_i^{j'}\} = \min\left\{\frac{\text{Leverage}_i^{j'}}{\text{Leverage}_i^{j}}, \frac{\text{Leverage}_i^{j}}{\text{Leverage}_i^{j'}}\right\} = \frac{\min\{\text{Leverage}_i^j, \text{Leverage}_i^{j'}\}}{\max\{\text{Leverage}_i^j, \text{Leverage}_i^{j'}\}}$$

Measure of Symmetry

→ Pr(Exclusion) = f(Leverage Asymmetry)

(+)

Table 2: Molecules, Products, and Key Dates in the Analytical Sample.

(1) Product	(2) Type	(3) Manufacturer	(4) Key dates FDA approval	(5) Key dates Earliest claim	(6) Analysis period
		Bevacizumab			
Avastin	Reference	Genentech	2004	2015	2019-2021
Mvasi	Biosimilar	Amgen	2017	2019	2019-2021
Zirabev	Biosimilar	Pfizer	2019	2020	2020-2021
Alymsys	Biosimilar	Amneal	2022	-	-
Vegzelma	Biosimilar	Celltrion	2022	-	-
Avzivi	Biosimilar	Sandoz	2023	-	-
		Epoetin Alfa			
Epogen/Procrit	Reference	Amgen/J&J	1989	2016	2018-2021
Retacrit	Biosimilar	Pfizer	2018	2018	2018-2021
		Filgrastim			
Neupogen	Reference	Amgen	1991	2015	2015-2021
Zarxio	Biosimilar	Sandoz	2015	2015	2015-2021
Nivestym	Biosimilar	Pfizer	2018	2018	2018-2021
Releuko	Biosimilar	Kashiv	2022	-	-
Tanvex	Biosimilar	Nypozi	2024	-	-
		Infliximab			
Remicade	Reference	J&J	1998	2015	2018-2021
Inflectra	Biosimilar	Pfizer	2016	2018	2018-2021
Renflexis	Biosimilar	Merck	2017	2018	2018-2021
Ixifi	Biosimilar	Pfizer	2017	-	-
Avsola	Biosimilar	Amgen	2019	2020	2020-2021
		Pegfilgrastim			
Neulasta	Reference	Amgen	2002	2015	2018-2021
Fulphila	Biosimilar	Mylan	2018	2018	2018-2021
Udenyca	Biosimilar	Coherus	2018	2019	2019-2021
Ziextenzo	Biosimilar	Sandoz	2019	2020	2020-2021
Nyvepria	Biosimilar	Pfizer	2020	2021	2021-2021
Fylnetra	Biosimilar	Amneal	2022	-	-
		Rituximab			
Rituxan	Reference	Genentech	1997	2019	2019-2021
Truxima	Biosimilar	Teva	2018	2019	2019-2021
Ruxience	Biosimilar	Pfizer	2019	2020	2020-2021
Riabni	Biosimilar	Amgen	2020	2021	2021-2021
		Trastuzumab			
Herceptin	Reference	Genentech	1998	2015	2019-2020
Ogivri	Biosimilar	Mylan	2017	2020	2020-2021
Herzuma	Biosimilar	Teva	2018	2020	2020-2021
Kanjinti	Biosimilar	Amgen	2019	2019	2019-2020
Trazimera	Biosimilar	Pfizer	2019	2020	2020-2021
Ontruzant	Biosimilar	Merck	2019	2020	2020-2021
Accord	Biosimilar	Hercessi	2024	-	-

Filgrastim

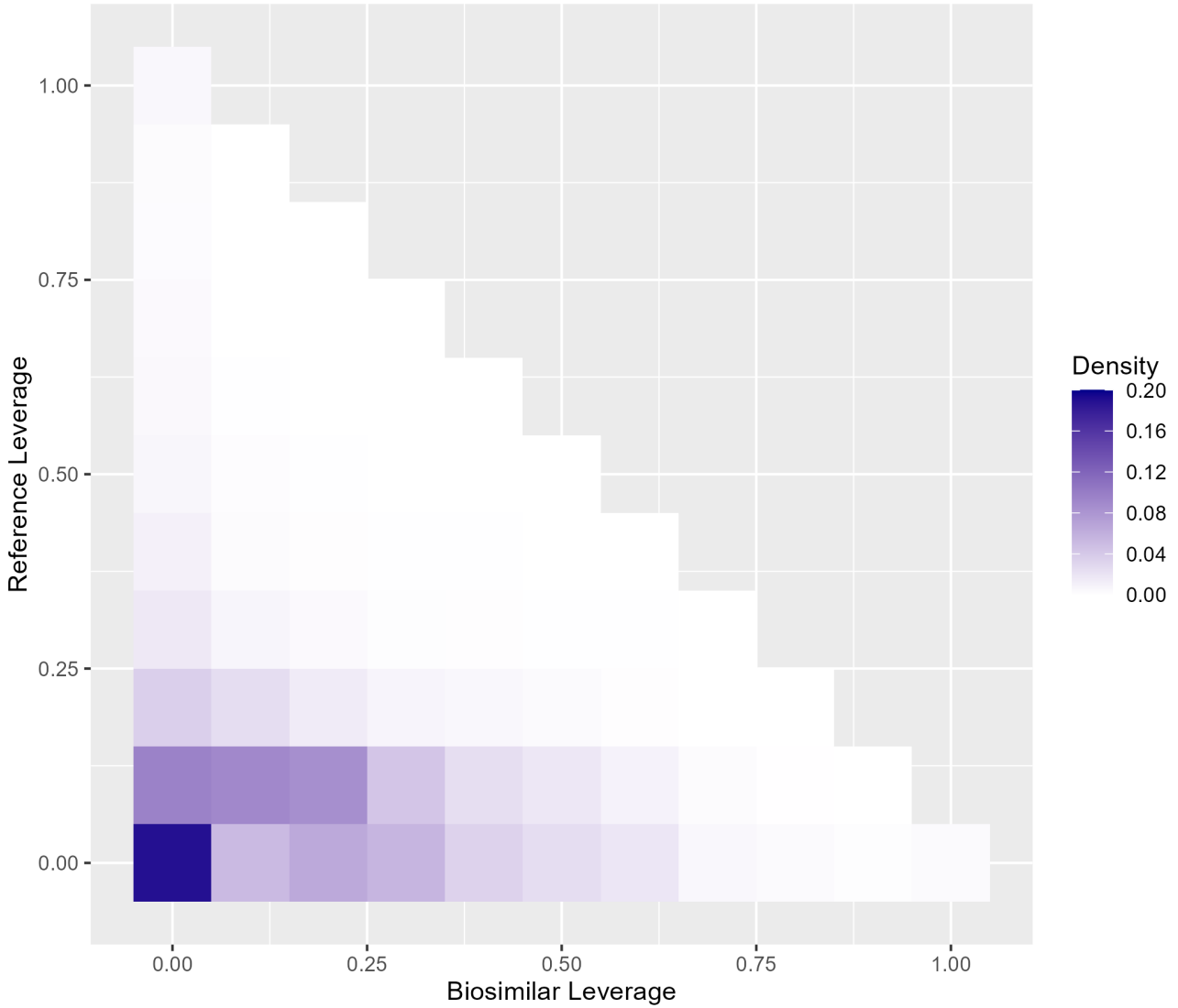
Neupogen	Reference	Amgen	1991	2015	2015-2021
Zarxio	Biosimilar	Sandoz	2015	2015	2015-2021
Nivestym	Biosimilar	Pfizer	2018	2018	2018-2021

Primary analysis: aggregate “biosimilar sector”

Observation level (N=24,815):

Molecule / clinic / year / **reference v biosimilar**

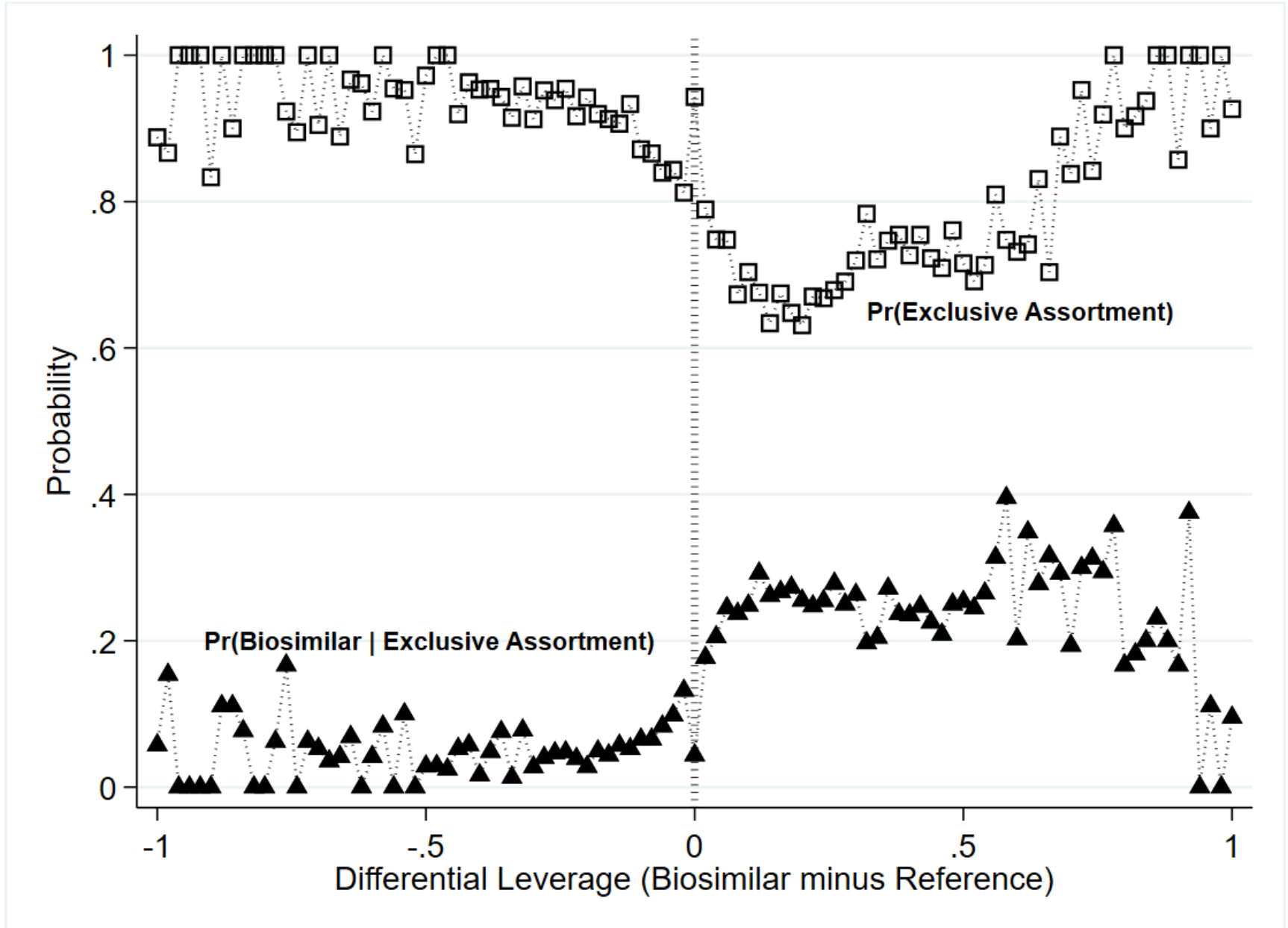
$$\text{Leverage}_{mjit} = \frac{\text{Clinic's manufacturer-specific adjacent spending}_{mjit}}{\text{Clinic's total adjacent spending}_{mit}}$$



Exclusive Assortment in 4/5 Clinics

Table 1: Clinic Assortment Types and Biosimilar Use by Molecule.

Molecule	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
		Exclusive Assortment				Non-exclusive Assortment		
	N	Preva-	Biosimilar Share			Preva-	Biosimilar Share	
		lence	Clinics	Claims	HHI	lence	Claims	HHI
Bevacizumab	5,687	91%	5%	2%	96%	9%	56%	96%
Epoetin Alfa	3,399	75%	17%	21%	100%	25%	40%	100%
Filgrastim	3,931	83%	36%	42%	98%	17%	67%	98%
Infliximab	4,772	80%	7%	2%	98%	20%	25%	94%
Pegfilgrastim	2,318	62%	23%	11%	92%	38%	30%	90%
Rituximab	2,968	81%	8%	11%	95%	19%	56%	91%
Trastuzumab	1,110	66%	32%	29%	92%	34%	45%	94%
Total	24,185	**80%**	15%	12%	97%	**20%**	45%	95%


1
.8
.6
.4
.2
0
Probability
Pr(Exclusive Assortment)
Pr(Biosimilar | Exclusive Assortment)
-1
-.5
0
.5
1
Differential Leverage (Biosimilar minus Reference)

Assortment Indicators

Leverage asymmetry, Differential leverage (biosim minus ref)

$$y_{mit} = \beta \cdot f(\text{Biosimilar Leverage}_{mit}, \text{Reference Leverage}_{mit}) + \alpha \cdot \text{Scale}_{mit} + \gamma \cdot \#\ \text{Biosimilar Products}_{mt} + \delta_{mi} + \theta_m \cdot t + \epsilon_{mit},$$

Molecule/clinic FEs

Molecule-specific time trends

Shift-Share Identification

- Intuition:
  - Drug maker sells cancer and cardiovascular drugs
  - Launches new cardiovascular drug
  - Launch increases the maker's leverage wrt clinics that serve both cancer and cardiovascular needs, not wrt those that serve only cancer

- Formulation: $\mathrm{IV}^{j}_{mit} = \sum_{k \in \mathcal{K}} \theta_{kmit} \cdot \log(1 + \mathrm{Revenues}_{-ikjt})$

  - Shares , stable clinic emphasis on drug class k (=1,..,24)
  - Shifts (Revenues), market-wide class-k portfolio strength

Table A.2: First-Stage Regressions: Instrumental Variables for Reference and Biosimilar Leverage

	(1) Reference Leverage	(2) Biosimilar Leverage	(3) Leverage Asymmetry	(4) Differential Leverage
IV_{Ref}	0.012	-0.004	0.037	-0.014
	(0.001)	(0.000)	(0.001)	(0.001)
	[0.000]	[0.000]	[0.000]	[0.000]
IV_{Biosim}	-0.003	0.015	0.029	0.020
	(0.000)	(0.000)	(0.001)	(0.001)
	[0.000]	[0.000]	[0.000]	[0.000]
IV_{RoI}	-0.004	-0.007	-0.005	-0.002
	(0.001)	(0.001)	(0.001)	(0.001)
	[0.000]	[0.000]	[0.000]	[0.099]
$IV_{Ref} \times IV_{Biosim}$			-0.004	-0.000
			(0.000)	(0.000)
			[0.000]	[0.000]
Scale	0.011	0.010	0.015	-0.002
	(0.002)	(0.001)	(0.003)	(0.003)
	[0.000]	[0.000]	[0.000]	[0.502]
# Products	0.004	0.056	0.059	0.056
	(0.002)	(0.002)	(0.006)	(0.003)
	[0.038]	[0.000]	[0.000]	[0.000]
N	22,411	22,411	22,411	22,411
F	86.29	2,023.39	233.34	1,604.59

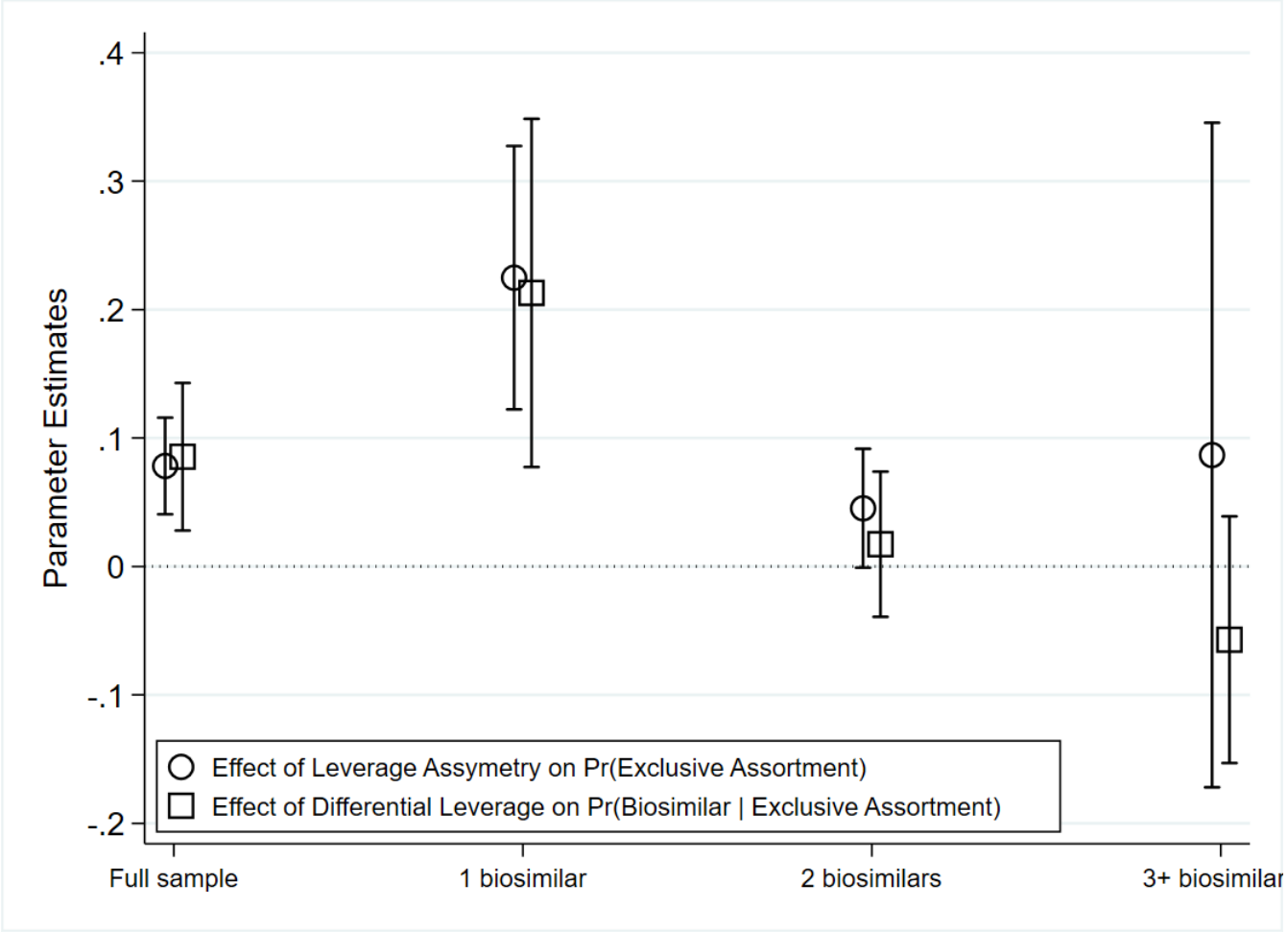
Δ 1 SD Diff. Lev → Δ Pr(Biosim | Excl. Assort) = 0.007

Table 2: Leverage Effects on Exclusive Assortment and Biosimilar Choice.

Outcome:	(1) Pr(Exclusive Assort.) OLS	(2) Pr(Exclusive Assort.) IV	(3) Pr(Biosimilar | Excl. Assort.) OLS	(4) Pr(Biosimilar | Excl. Assort.) IV
Leverage Asymmetry	0.034	0.078		
	(0.011)	(0.019)		
	[0.003]	[0.000]		
Differential leverage			0.102	0.085
			(0.016)	(0.029)
			[0.000]	[0.004]
Scale	-0.021	-0.022	0.004	0.003
	(0.002)	(0.002)	(0.001)	(0.001)
	[0.000]	[0.000]	[0.011]	[0.014]
# Biosimilar products	-0.143	-0.145	0.002	0.003
	(0.009)	(0.009)	(0.004)	(0.005)
	[0.000]	[0.000]	[0.693]	[0.536]
N	22,431	22,431	16,850	16,850

Δ 1 SD Lev. Assym. → Δ Pr(Excl. Assort) = 0.028

Leverage effects are strongest in markets with a single biosimilar competitor



Within-biosimilar choice: Leverage matters, but entry order matters more

Table 3: Drivers of Within-Biosimilar Product Selection.

	(1)	(2)	(3)
	Full	Assortment	
	Sample	Non-exclusive	Exclusive-biosimilar
Leverage	0.280	0.265	0.265
	(0.024)	(0.086)	(0.150)
	[0.024]	[0.086]	[0.150]
First Mover	0.307	0.291	0.259
	(0.000)	(0.000)	(0.028)
	[0.000]	[0.000]	[0.028]
Entry Lag	-0.039	-0.042	-0.048
	(0.000)	(0.001)	(0.019)
	[0.000]	[0.001]	[0.019]
N	11,774	6,975	4,799

Discussion points

1. The economics of biosimilars are very different to those of generics
    - *Generic markets:*
        + Defensive incumbent + aggressive generic fringe
        + After pay-for-delay, flood gates open
        + No multi-product considerations
    - *Biosimilar markets:*
        + An oligopoly
        + Multi-product considerations are first order
        + Flood gates never really open, penetration by drip

2. Commercial relationships (leverage) as a barrier of entry
    - Why is Pfizer prioritizing biosimilars over original biologics?
        + Comparative advantage in terms of leverage
    - Can any firm penetrate the biosimilar market?
        + Unlikely. The "right" commercial capabilities are needed. We can probably predict biosimilar entry at the firm level.
    - Is the amount of biosimilar innovation a matter of clinical trial cost?
        + It may be more about monetization (extracting value from successful launches)

Thank you 🙏🙏🙏🙏