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The US Biosimilar Market: Stunted Growth and Possible Reforms

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US Prescription Drug Spending

- Net spending in 2016
  - CMS NHEA estimate (retail only): $329 billion
  - ASPE projection (retail and non-retail): $477 billion

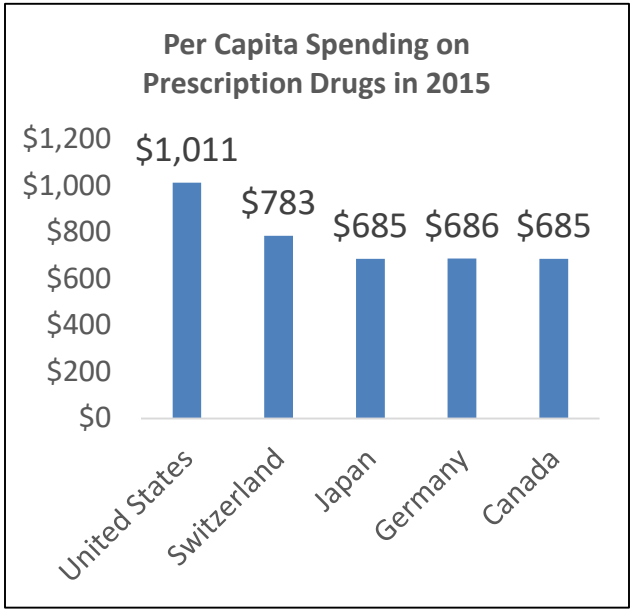
-Pew Charitable Trusts (2018).

- CMS NHEA projection (2017-2026)
  - 6% annual increase in net retail spending
  - Faster than any other good or service

-Cuckler et al. Health Aff (2018).

- 2015 international per capita comparison
  - US: $1,011
  - Mean of Canada, France, Germany, and Japan: $652

-OECD (2017).



Catalyst: Increasing Prescription Drug Prices

- Brand-name drugs
  - Rising launch prices
    - Median annual list price of new cancer medication
      - 2017: $160,000
      - 2011: $101,000 (2013 dollars)

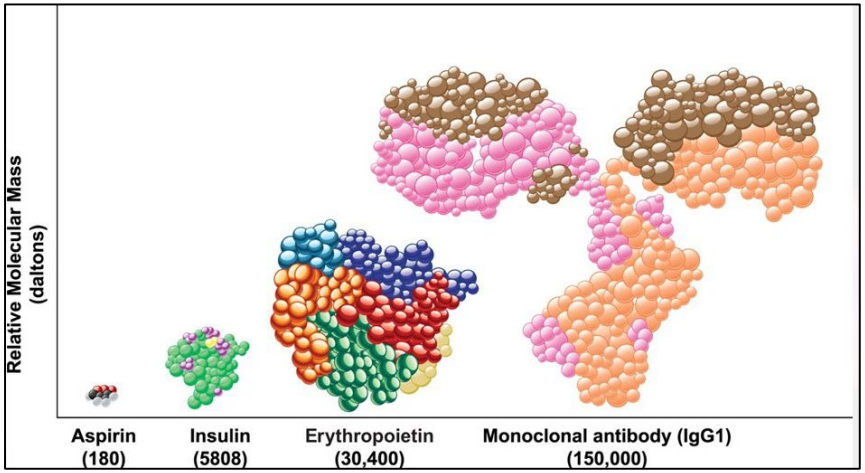
        - IQVIA (2018).
  - Markups
    - 2019: List prices of more than 250 drugs by an average of 6.5%

      -Bloomberg (2016).
  - 2008-2016
    - List prices for commonly used brand-name drugs increased 208%

      -Express Scripts (2017).
- Select generic drugs
  - For relatively uncommon conditions: *e.g.*, pyrimethamine (Daraprim)
  - Coupled to patented delivery systems: *e.g.*, epinephrine autoinjector (EpiPen)

Biologics: Large Molecules, Large Price Tags

- Large complex molecules or molecular mixtures derived from living systems



-Mellstedt. EJC Supplements (2017).

  - Not easily characterized
  - Often physician-administered


BUSINESS

FDA Approves Pioneering Cancer Treatment With $475,000 Price Tag

Novartis's Kymriah gets nod for some leukemia patients; uses body's own cells to fight cancer

-Wall Street Journal (2017).

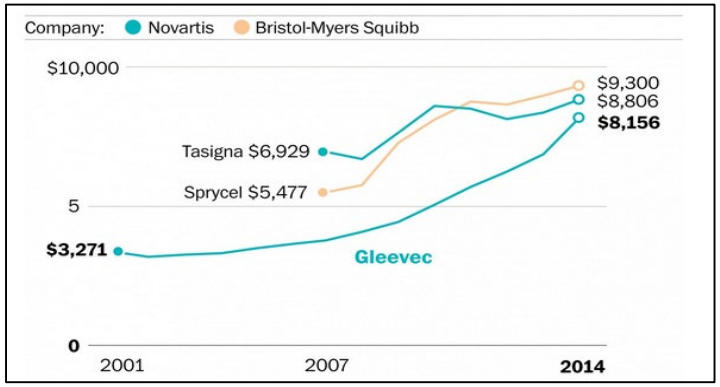
- Key driver of increased prescription drug spending
  - Expensive: several exceed $100,000 per-patient per-year
  - 40% of US pharmaceutical expenditures, but only used by 2% of Americans

-FDA (2018).

  - Increasing proportion of drug approvals

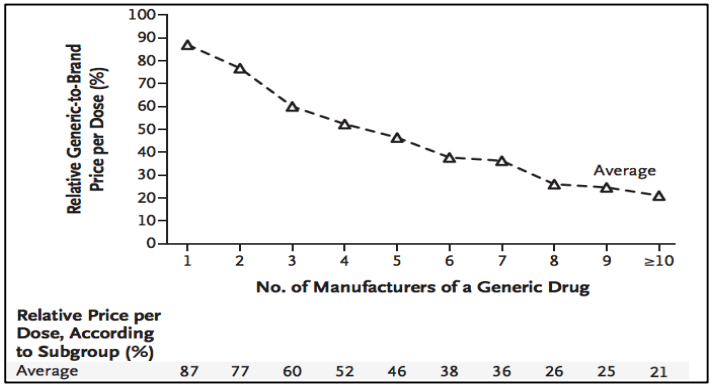
High Drug Prices: Does Competition Help?

- Limited evidence that brand-brand competition lowers prices (notable exception: hepatitis C drugs)



-Washington Post (2017).

- The only type of competition that consistently and substantially lowers prescription drug prices occurs from generic drugs



-Dave et al. NEJM (2017).

Hatch-Waxman Act's ANDA Pathway

- Drug Price Competition and Patent Term Restoration Act (i.e., Hatch-Waxman Act)
  - Passed in 1984
  - Abbreviated new drug application (ANDA) pathway for versions of approved drugs made by different manufacturers
    - Applies to small-molecule drugs
    - Basis of approval: showing that the "generic" drug has the same active ingredient, dosage form, and strength, as well as the same absorption of the active ingredient at the target site
- Coupled with state drug product selection laws that authorize (or mandate) pharmacists to substitute prescriptions for brand-name drugs with generics
- Incredible success story
  - 1984-2017: 19% $\rightarrow$ 89% of prescriptions dispensed with a generic

    -CBO (1998); AAM (2017).
  - Possible price reductions: >80%
  - $1.6 trillion in savings over past decade

BPCIA Pathway

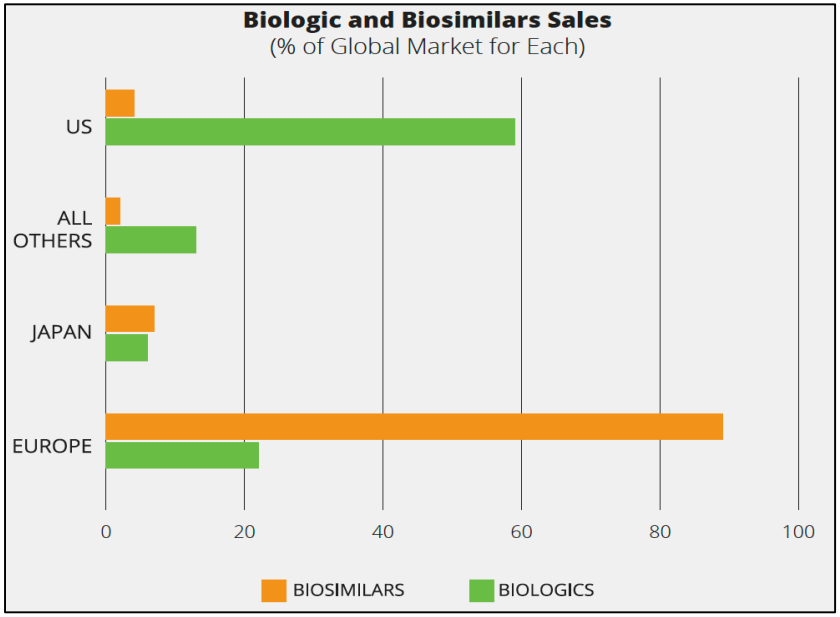
- Biosimilars: versions of approved biologics by different manufacturers
  - Analogous but not equivalent to generic small-molecule drugs
- Biologics Price Competition and Innovation Act (BPCIA)
  - Enacted as part of the Affordable Care Act in 2010
  - Created an abbreviated approval pathway for follow-on biologics
    - Similar but more extensive than pathway for small-molecule generics
  - Two possible approvals
    - Biosimilar: “highly similar” and “no clinically meaningful differences” with regard to “safety, purity, and potency”
    - Interchangeable: biosimilar and “can be expected to produce the same clinical result…in any given patient”
      - Required assessment of safety of switching between originator biologic and follow-on biologic
  - Exclusivity: 12 years=originator; 1 year=interchangeable

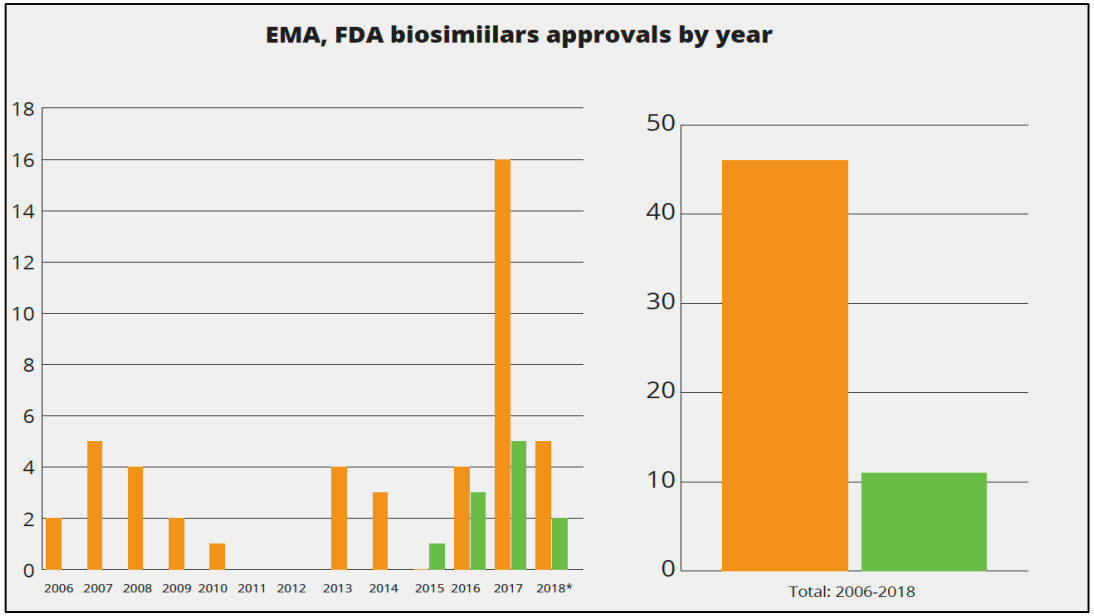
US Biosimilars (as of November 1, 2018)

Biosimilar nonproprietary name	Biosimilar proprietary name	Approval year	Manufacturer	Biosimilar wholesale acquisition cost	Originator proprietary name	Originator wholesale acquisition cost	Savings (%)	Reason not marketed
Adalimumab–adbm	Cyltezo	2017	Boehringer Ingelheim	–	Humira	$4,872.03 40 mg/0.8 mL kit (2×)	–	Patent Litigation
Adalimumab–adaz	Hyrimoz	2018	Sandoz[c]	–	Humira	$4,872.03 40 mg/0.8 mL kit (2×)	–	Patent Settlement
Adalimumab–atto	Amjevita	2016	Amgen	–	Humira	$4,872.03 40 mg/0.8 mL kit (2×)	–	Patent Settlement
Bevacizumab-awwb	Mvasi	2017	Amgen	–	Avastin	$796.94 25 mg/mL	–	Patent Litigation
Epoetin alfa-epbx	Retacrit	2018	Hospira[b]	$330.90 3,000 u/mL (10×)	Epogen	$497.40 3,000 u/mL (10×)	34	
				$1,764.80 40,000 u/mL (4×)	Procrit	$4115.44 40,000u/mL (4×)	57	
Etanercept-szzs	Erelzi	2016	Sandoz[c]	–	Enbrel	$4,872.00 50 mg/mL (4×)	–	Patent Litigation
Filgrastim-sndz	Zarxio	2015	Sandoz[c]	$275.66 300 µg/0.5 mL	Neupogen	$333.70 300 µg/0.5 mL	17	
Filgrastim-aafi	Nivestym	2018	Hospira[b]	$219.00 300 µg/0.5 mL	Neupogen	$333.70 300 µg/0.5 mL	34	
Infliximab-dyyb	Inflectra	2016	Celltrion[d]	$946.28 100 mg	Remicade	$1,167.82 100 mg	19	
Infliximab-abda	Renflexis	2017	Samsung Bioepsis	$753.39 100 mg	Remicade	$1,167.82 100 mg	36	
Infliximab-qbtx	Ixifi	2017	Pfizer	–	Remicade	$1,167.82 100 mg	–	Manufacturer Choice
Pegfilgrastim-jmdb	Fulphila	2018	Mylan	$4,175.00 6 mg/0.6 mL	Neulasta	$6,231.06 6 mg/0.6 mL	33	
Trastuzumab-dkst	Ogivri	2017	Mylan	–	Herceptin	$1,558.42 150 mg	–	Patent Settlement

13 approved; 6 marketed; 19%-57% list price savings; variable uptake

Contrasting the European Experience





- Biosimilars Forum and Biosimilar Medicines (2019).

Manufacturing Impediments

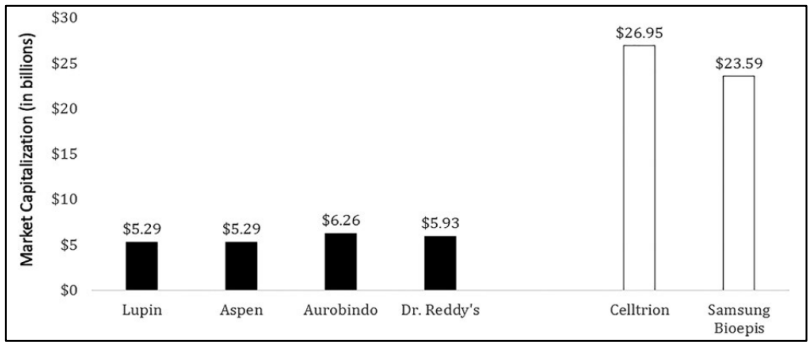
- Production costs: greater than for small-molecule drugs
  - 8-10 years, $100-$200 million vs. 3-5 years, $1-$5 million

-FTC (2009).

- Technical expertise: beyond the capacity of many generic drug makers
- Trade secrets: "would be competitors…must attempt to reverse-engineer complex and idiosyncratic manufacturing techniques."

-Price & Rai. Science (2015).

- Characteristics of biosimilar manufacturers
  - November 2018 : 8 manufacturers of 13 biosimilars
    - Also manufacture originator biologics: 3
    - Subsidiaries of originator manufacturers: 2
    - High market cap



-Sarpatwari et al. CPT (2019).

Regulatory Impediments-I

- Approval standards: comparative clinical studies
  - Required when there is residual uncertainty about biosimilarity
    - Pivotal trial for filgrastim (Neupogen): 210 patients
    - Compartive clinical study for filgrastim-sndz (Zarxio): 218 patients
- Patent dance: complex process prior to follow-on biologic entry specified in BPCIA clarified in *Sandoz v. Amgen*
  - "Shall provide" notice to originator biologic of intent to enter the market no later than 180 days before commercial marketing
    - Question: Pre- or post-FDA approval?
    - Court: May be given pre-FDA approval
  - "Shall provide" confidential copy of FDA application
    - Question: Injunctive remedy?
    - Court: No

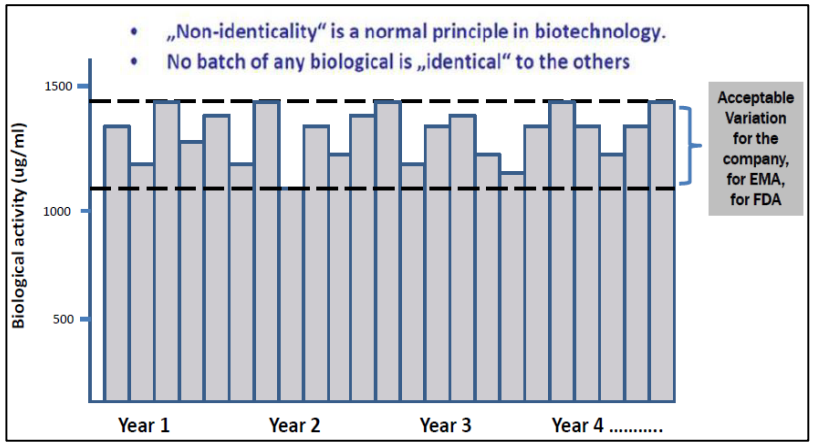
Regulatory Impediments-II

- Reitence to declare interchangeability
  - Concern over immunogenicity (i.e., provoking an immune response)

"Because unlike most of our small molecule drugs, the body recognizes these large protein molecules that are biosimilars and often in some people will make an immune response. That the concern has been is that this continued switching could raise that immunity, sort of provide a booster effect and cause unthwarted effects."

-Woodcock (2015).

- But lack of evidence
  - Switching studies
  - Safe use in Europe for over a decade



- Same risk from intra-product batch variation?
  - Case: interferon beta and thrombotic microangiopathy

Market Impediments

- Rebate trap
  - Making rebate conditional upon exclusive sourcing
  - Capitalizes on difficulty of switching patients from product A to B

		Post-Biosimilar	
	Pre-Biosimilar	50% of Patients Switch	100% of Patients Switch
Reference biologic list price, US $	50 000	50 000	50 000
Reference biologic postrebate price, US $	25 000	NA (no longer offering rebate)	NA (no longer offering rebate)
Biosimilar price, US $	NA	10 000	10 000
Patients taking branded biologic, No.	1000	500	0
Patients taking biosimilar, No.	NA	500	1000
Payer cost, US $	25 000 000	30 000 000	10 000 000

-Hakim & Ross. JAMA (2017).

- Physician and patient skepticism
  - 72% of 81 surveyed Canadian rheumatologists reported being unlikely or very unlikely to offer a biologically naïve patient a biosimilar over an originator
  - Possibly fueled by FDA rule requiring unique suffixes for non-proprietary names

Patent Settlements: Anticompetitive?

PRESS RELEASE

Labaton Sucharow Files Class Action against AbbVie And Other Drugmakers, Alleging Anti-Competitive Practices to Block Competition for Blockbuster Drug Humira in the United States

Published: Mar 19, 2019 10:00 a.m. ET

-MarketWatch (2019).

- Adalimumab (Humira)
  - First approved by FDA in 2002
  - Global sales in 2016: Over $16 billion

Pharma

Humira biosimilars catch fire in Europe and could take half the market in a year: report

-FiercePharma (2019).

- Patent settlements
  - Amgen's adalimumab-atto (Amjevita) in October 2017
  - Sandoz's adalimumab-adaz (Hyrimoz) in October 2018
  - Known terms: allowed EU marketing; delayed US marketing until 2023
- Patient Right to Know Drug Prices Act: enacted in 2018

Possible Solutions

Manufacturing	Regulatory	Market
Mandatory disclosure of trade secrets upon expiry of market exclusivity	Coordinated review with other regulators (e.g., EMA)	Greater use of *inter partes* review to challenge questionable patents
Government manufacturer or government support of non-profit manufacturer	Rigorous post-approval surveillance	Mandatory disclosure of product-related patents in "Purple Book"
	Modified state drug product selection laws to authorize select biosimilar substitution	Mandatory reporting of all patent settlements between originator and follow-on manufacturers to the FTC
	Price-setting following expiry of market exclusivity	Removal of unique non-proprietary name suffixes
		Prohibiting exclusive dealing conditions