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

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

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

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)
    - XVA (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

- Not easily characterized
- Often physician-administered

- 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
  - Increasing proportion of drug approvals

High Drug Prices: Does Competition Help?

- Limited evidence that brand-brand competition lowers prices (notable exception: hepatitis C drugs)
- The only type of competition that consistently and substantially lowers prescription drug prices occurs from generic drugs

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% → 89% of prescriptions dispensed with a generic
  - $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)**

[Table with approval dates, manufacturers, and market status]

**Contrasting the European Experience**

- Biologics and Biosimilars share 8% of US market for line.
- Biosimilars approvals by year.

[Graph showing biosimilars approvals by year]

**Manufacturing Impediments**

- Production costs: greater than for small-molecule drugs
  - 8-10 years, $100-$200 million vs. 3-5 years, $1-$5 million
- Technical expertise: beyond the capacity of many generic drug makers
- Patent thickets: adalimumab (Humira) >100 patents

**Regulatory Impediments-I**

- Approval standards: comparative clinical studies
  - Required when there is residual uncertainty about biosimilarity
    - Pivotal trial for filgrastim (Neupogen): 210 patients
    - Comparative 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.”
  - 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

<table>
<thead>
<tr>
<th>Pre-Biosimilar</th>
<th>Post-Biosimilar</th>
<th>50% of Patients Switch</th>
<th>100% of Patients Switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference biologic list price, US $</td>
<td>50 000</td>
<td>50 000</td>
<td></td>
</tr>
<tr>
<td>Reference biologic probability price, US $</td>
<td>25 000</td>
<td>NA (no longer offering rebates)</td>
<td></td>
</tr>
<tr>
<td>Biosimilar price, US $</td>
<td>NA</td>
<td>50 000</td>
<td></td>
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<tr>
<td>Patients taking biosimilar, No.</td>
<td>1000</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>Patients taking biosimilar, No.</td>
<td>NA</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Prescriber cost, US $</td>
<td>25 000 000</td>
<td>10 000 000</td>
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- 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

Possible Solutions

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<tr>
<th>Manufacturing</th>
<th>Regulatory</th>
<th>Market</th>
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<tbody>
<tr>
<td>Mandatory disclosure of trade secrets upon expiry of market exclusivity</td>
<td>Coordinated review with other regulators (e.g., EMA)</td>
<td>Greater use of inter partes review to challenge questionable patents</td>
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<td>Government manufacturer or government support of non-profit manufacturer</td>
<td>Rigorous post-approval surveillance</td>
<td>Mandatory disclosure of product-related patents in “Purple Book”</td>
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<td>Modified state drug product selection laws to authorize select biosimilar substitution</td>
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<tr>
<td>Price-setting following expiry of market exclusivity</td>
<td>Removal of unique non-proprietary name suffixes</td>
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<td>Prohibiting exclusive dealing conditions</td>
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Patent Settlements: Anticompetitive?

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