Biosimilars: theory, policy, and preliminary evidence

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Biologics (a.k.a biopharmaceuticals)

Derived from living cells: enzymes, antibodies (proteins), vaccines; complex molecules

Heterogeneous: molecules not identical to one another

Examples: genetically engineered recombinant proteins and monoclonal antibodies

Large portion of newly approved therapies for chronic inflammatory diseases, cancer: Bevacizumab (Avastin)
Biologics: structure and production

- Structurally larger molecules
- Average molecular weight of biologic = 4000 Daltons (Da) [non-glycosylated proteins] to > 140 000 Da [monoclonal antibodies]
- Average molecular weight of small molecule chemical pharmaceuticals = 160 to 800 Da
- Harder to produce and reproduce than small molecule drugs, commensurately expensive

← Lipitor (Atorvastatin) vs. Herceptin (Trastuzumab) →
Monoclonal antibodies: 50,000
Biosimilars: drugs that are clinically equivalent to licensed biological medical products made using genetically engineered living cells (such as enzymes, antibodies, and vaccines).

- Intended to have the same mechanism of action as the original biological medicine and to be used in treating the same disease.
- Development based on comparability to reference biological product.
- Legal term introduced in Europe (2003): “similar biological medicinal product”
- In US, often referred to as “follow-on-biologics”
Chemical generics

• Hatch-Waxman 1984; fantastic success
• NDA, New Drug Application, is method of entry
• ANDA is pathway for generic entry at low F
• Demonstrate bioequivalence to reference product
• Not showing efficacy
• (Brands get exclusivity extension if FDA slow to approve)
• FDA certifies that products are homogeneous
• => Zero profit industry and consumers win

The first generic entrant that challenges a brand’s unexpired patent and wins earns 6 months of generic exclusivity

Overcomes free-riding on effort to defeat patent

Important to note that rules build in profit inducement
Existing research findings H-W

Effect: lots of generic entry (Grabowski and Vernon)
Biggest selling drugs routinely >10 entrants
Entry is immediate

Price effects are large (Salkever, Berndt and Aitken)
Entry at 77-80% of original brand price
Falls quickly over next two years
In markets with many entrants, final generic price may be as low as 10% of original brand price

Quantity effects are large (Berndt and Aitken)
Estimate a 92% generic fill rate in 2009
Share of prescriptions where a generic is available is 81%
Net fill rate is 74.5%
Figure 1.—Lorazepam price trend
<table>
<thead>
<tr>
<th>Product</th>
<th>Class</th>
<th>Generic launch</th>
<th>Market size at entry (in 2000 $ m)</th>
<th>Generic share 12 months after generic entry (%)</th>
<th>Generic Price 12 months after generic entry to branded price pre-entry (%)</th>
<th>Number generics 12 months after generic entry</th>
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<tbody>
<tr>
<td>Zantac</td>
<td>Gastrointestinal</td>
<td>Jul-97</td>
<td>1,856.94</td>
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<td>Tagamet</td>
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<td>Naprosyn</td>
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<td>697.05</td>
<td>85</td>
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<td>18</td>
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<tr>
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<td>Lopressor</td>
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<td>Oct-93</td>
<td>371.26</td>
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<td>Lodine</td>
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<td>Feb-97</td>
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<td>Voltaren</td>
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<td>Glucotrol</td>
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<td>May-94</td>
<td>288.60</td>
<td>58</td>
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</tbody>
</table>
Desire to replicate

Chemical generics are huge success story
   In absolute terms
   Relative to other countries

- Spending on prescription drugs dropped in real terms for the first time in 2012
- Biologic growth is meanwhile 12% p.a.
- Moreover, biologic products are expensive for individual consumers

Could we stimulate generic entry for biologics, replicate H-W, and save the consumer and the taxpayer money?
Expected outcome

- Previous economics literature: Grabowski
- Biosimilar fixed cost of entry will be higher than generic due to complexity
- Biosimilar will (at present) be more differentiated than generic due to complexity
- Research capabilities needed are much more sophisticated
- Manufacturing fixed investment higher
- Manufacturing requires more safety, tighter tolerances, more steps, more complexity

=> Basic model yields, relative to chemical generics:
   Less entry
   Smaller price drops due to biosimilar entry
However, turn down a 30% savings because it’s not 80%?
Which markets have generics?

Do not expect all markets to attract generic entry. (Scott Morton 1999)

Firm \( i \) enters market \( k \) if

\[
E(\pi_{ik}) = (p_k - c_{ik})q_{ik} - F_{ik} > 0
\]

F will be relatively constant across market size, though we expect it to vary by molecule, but \( q \) is small in small markets

Can estimate size cutoff below which there will be no generic entry; function of \( F \)

F is policy choice; level of \( F \) will determine how many markets have generic competition
Biosimilar pathway

Vigorous lobbying for many years---
Innovator biologics do not want competition: perpetual monopoly more lucrative
  Ask for long guaranteed exclusivity period
  Ask for high standard of similarity
  Patients might die; no risk is acceptable
HMO/insurer (and taxpayer):
  Elimination of risk raises F
  High enough F means no entry and no cost savings
BLA, Biologics License Application, is innovator pathway
ACA authorizes “abbreviated pathway” for biosimilars
ACA also provides 12 years of innovator exclusivity
Pathway design

ACA creates two pathways

  Interchangeable: identical, pharmacy may substitute
  Substitutable: similar, physician must substitute

(Confusingly, the Europeans use the same terms with opposite meanings)

FDA final guidance on standards has not been published
Draft guidance documents released in February, 2012
  => No US entry to date

FDA activity

• 47 Pre-IND meeting requests for proposed biosimilar products to
  11 reference products
• 30 Pre-IND sponsor meetings held to date
• 12 INDs for proposed biosimilars
Biosimilarity

FDA definition of biosimilarity:

1) Biological product is highly similar to reference product notwithstanding minor differences in clinically inactive components

2) No clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of product

*FDA will not provide guidance on proving interchangeability until after first biosimilar is approved*
FDA on Interchangeability:

- BPCI Act gives FDA the authority (optional) to designate a biosimilar as “interchangeable” with its reference product.
- 1st biological product to be licensed as interchangeable is granted a *period of exclusivity* (similar to H-W).
- During exclusivity period, a subsequent biological product relying on same reference product cannot be licensed as interchangeable.
- Exclusivity calculus is based on date of approval, date of first commercial marketing, and patent litigation milestones.
- Explicit recognition here that entry of a homogeneous product produces no rents for the entrant; rules attempting to create financial incentive for entry.
Demonstrating Biosimilarity

Clinical and laboratory tools are improving rapidly, but they don’t ‘draw’ the molecule:

- **Spectroscopy:**
  - Absorption of regular light by different proteins
    - infra-red light fluorescent or phosphorescent light
- **Mass spectrometry:** cut up molecule and get distribution of weights of atoms
- **Calorimetry:** do two samples heat up at same rate?
- **Chromatography**
  - Which proteins are hydrophobic?
  - Which proteins have what sizes?
- **Nuclear magnetic resonance spectroscopy**
  - measures presence of atoms: “quantitative,” “fingerprint”
Biosimilar manufacturing issues

Master Cell Banks (proprietary)
  Original generic material
Culture and Fermentation Systems
  In what medium does the cell grow?
Purification
  At what stage, through which filter?
Quality Control
  Method for assessing product
Patient Delivery and Monitoring

Complex manufacturing, relying on significant levels of tacit process knowledge. Disclosed to FDA only.
Complex production

Monoclonal Antibody Production

- Stimulate antigen & immunize
- Cell fusion
- Cloning
- Harvest
- Screening
- Purity

Phases:
- Phase I
- Phase II
- Phase III
- Phase IV
- Phase V
Complex production
Why can a manufacturer assure regulators that it can produce a consistent product across batches and production lines but claim it is impossible for other firms to produce a “biogeneric”? 
It is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product. However, minor modifications, such as N or C terminal truncations that will not have an effect on safety, purity, or potency, may be justified by the applicant.

Highly similar with fingerprint-like similarity permits a more selective and targeted approach to determine if biosimilar

-FDA 2012
Simple regulatory model

Market structure: one branded biologic (firm 1) and one potential biosimilar entrant (firm 2)

Differentiated Bertrand competition yields profits for the entrant of:

$$\pi_2 = (p_2 - c)D_2(p_1, p_2, \beta_2^k) - F^k$$

k can be high or low, H or L

Strength of differentiation between the brand and biosimilar: $$\beta_2^H$$ or $$\beta_2^L$$, is policy choice of regulator.

For example, $$\beta_2$$ could be own price coefficient in linear demand model

Fixed cost of entry is policy choice of regulator: $$F^H$$ or $$F^L$$
Comparative statics

Not focused on particular demand specification. Care about comparative statics

$\pi_2$ decreases in $F$: Higher fixed costs of entry for the biosimilar reduce profits, one for one.

$\pi_2$ decreases in $\beta_2$: Less differentiation (higher substitutability) reduces profits for the entrant, despite higher share

$\Rightarrow$ The “H” regime features lower profit for the entrant.

More intense price competition benefits consumers and requires greater fixed cost.
Choice of the regulator

Substitutability:
- Easier to prove, so low fixed cost, $F_L$
- More differentiation, $\beta_2^L$, so more variable profit

Interchangeability:
- More costly to prove because the drugs must be identical, so
- High fixed cost, $F_H$ and more homogeneous products
- More price competition, $\beta_2^H$ results in lower variable profit

Entrant clearly prefers substitutability as an entry strategy. It costs less and yields a stream of economic profit going forward.

Regulator chooses scheme, but biosimilar chooses whether, when, and which markets to enter based on profit.

Can think of interchangeability standard being $H$
Or, choice of strictness of substitutability standard being $H$ versus $L$
Entry models

Consider whether biosimilar entrant will choose to enter a given market: Replace $q$ (as in B-R) with market size times share, $S_r$ ($r=q/Q$)

Entrant enters if, in expectation: $$(p^k - c)S_r^k - F^k > 0$$

Consider threshold size required to induce the first (only) entrant, $S^*$

$S^*$ will vary with $k$. In particular, $S^{*H} > S^{*L}$

$S^*$ must be larger when margins are lower in order to cover the same fixed costs; $S^*$ must be larger for larger fixed costs.

See Berry (1992), Bresnahan and Reiss (1990/1), (pharma application: Scott Morton(1999))
Markets are heterogeneous

Choose a regulatory regime, k, to fix $S^*$

$S_i$ will vary across markets, with some $S_i > S^*$; therefore the existence of entry will vary across markets, when for market $i$:

$$(p_i^k - c_i)S_i r_i^k - F_i^k > 0 \Rightarrow S_i > S^*$$

Tradeoff:
In any particular instance, the consumer is better off with biosimilar entry of type H
But there is less entry in regime H. In H, more markets remain un-entered, for no welfare gain.

Empirical question, which effect dominates
Welfare comparison of H and L

We can calculate the differences in prices and consumer surplus for each market under regulatory rules L and H.

We can predict which markets $i$ will attract a biosimilar entrant:

- No entry under either regime: $S_i < S_{*L}$
- No entry under H, but entry under L if $S_{*L} > S_i > S_{*H}$
- Entry under either regime if $S_i > S_{*H}$

We need a distribution of market sizes, and a discount rate to sum up the surplus across markets and over time.
Rough sketch of comparison

Use list of products and sales from Rovira (2011), GABi online 29/6/2012, and UBS research. Clearly a subset. Global sales somewhat larger than US+EU

Market sizes that have entrants today in EU:

- **Somatropin**: 1.34 $b/year
- **Epo**: 5.07
- **Filgrastim**: 1.48

If F is similar across markets, take minimum $S_i$ and call that $S^*$: 1.34 billion

Assume shift from L to H causes $S^*$ to move from 5th to 30th percentile of the market size lists above. $S^* = $1.73 billion/yr

⇒ Total revenue in ‘newly’ un-entered markets: 9.46 Billion

Assume lost revenue is 20% of $9.46 = 1.9B

Offset by increased price competition in remaining markets with entry?

- 70B sales annually in remainder of the distribution
- 10% in additional price reduction (30% total) for benefit of $7B
Improvements

IMS data provide full distribution of markets
  EU vs US
European price data provide price competition for regime L
Accounting data provide estimate of $F$
  Previous literature largely focused on this question
  Considerable technological change
  Work to develop estimate of $F^H$
Estimate of $F^H$ will allow estimate of the percentile of the
distribution of markets affected by changing regime
Last component is intensity of price competition in $H$
  Structural
  Bounds implied by other parameters
Further complication

Suppose H mandated

Biosimilar entrant always has choice to enter as brand (“biobetter”)
  No reference product
  Normal fixed cost of BLA
  May have superior manufacturing technology and design relative to original (likely 25 years old)
  Guaranteed differentiation; less price competition

Suppose entry cost of brand is $F^B$
  If $F^B < F^*H$, then entrant will choose to enter as brand

Unless there is some additional un-modeled cost such as brand advertising offsets savings in fixed cost

=> Proliferation of brands or entry of biosimilars?
Additional policy options

Other concerns besides technical standard of substitutability:

Clearly any reduction in the fixed cost of entry while holding technical standards constant is good. Lower effective F will stimulate more entry and benefit consumers.

- Data sharing
- Mandated disclosure of manufacturing information

Policies that reduce effective differentiation benefit consumers provided there remain enough profits to induce entry

- Buying institutions
- Formularies
- Physician education
Entry in Europe

10-year data exclusivity period for both new chemical entities (NCEs) and new biological entities (NBEs) before generics and biosimilars can be approved.

Developed a pathway in 2003; first approval of biosimilars in 2006

Three types of molecules/markets have been entered

Fourteen approvals to date

Fewer unique manufacturers: 6+ “development programs”
Entry in Europe

Key:
- Somatropin biosimilars
- Epoetin alpha biosimilars
- Epoetin zeta biosimilars
- Neupogen biosimilars


Omnitrope, Valtropin
Binocrit, Epoetin alpha
Hexal, Absamed, Retacrit, Silapo

Ecotropin, Valtopin
Biogaran, Epoetin alpha
Hexal, Tevagrasim
Zarzio

Rheoscoras, Filgrastim Hexal
Nivestim

Yale SCHOOL OF MANAGEMENT
## 2009 Market Share of Biosimilars

<table>
<thead>
<tr>
<th></th>
<th>All Drugs</th>
<th>Biologics (Fract. Total)</th>
<th>Biosimilars (Fract. Total)</th>
<th>Biosimilars/Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>2996</td>
<td>643.6 (21.5)</td>
<td>24.6 (0.8)</td>
<td>3.8</td>
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<tr>
<td>Belgium</td>
<td>4320</td>
<td>972.2 (22.5)</td>
<td>34.0 (0.7)</td>
<td>3.5</td>
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<tr>
<td>Bulgaria</td>
<td>670</td>
<td>90.5 (13.5)</td>
<td>1.9 (0.2)</td>
<td>2.1</td>
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<td>Czech Rep.</td>
<td>1936</td>
<td>363.7 (18.8)</td>
<td>6.7 (0.3)</td>
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<td>Denmark</td>
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<td>Estonia</td>
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<td>0.5 (0.4)</td>
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<tr>
<td>Finland</td>
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<td>Hungary</td>
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<td>UK</td>
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<td>62.9 (0.4)</td>
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</table>
Sales of originators vs. biosimilars in German markets (Rovira 2011)
Case study: Omnitrope’s strategy focuses on its key advantage, discounted price, to counter skepticism around biosimilars

On average, Omnitrope’s price is around 20% below the price of Genotropin. These discounts are considerably less aggressive than what is seen in small molecule generic markets so far.

- Although Omnitrope is priced at a discount to Genotropin, there has been resistance to its uptake due to:
  - Concerns about the efficacy and safety of the product
  - The pediatric indication it serves
- The discount is not substantial enough to outweigh the risk for many stakeholders
- Nevertheless an FRP is in preparation.

Source: Simon-Kucher & Partners

OHE Biosimilars Conference
June 2, London

Towse, 2010
Filgastrim vs. Biosimilar: 2009 (Rovira (2011))
Case study

English purchase data on web
Two growth hormone products
  - Genotropin 5.3mg and 12mg cartridges
  - Omnitrope 5 and 10mg cartridge
Compare price per milligram
Track quantities over time

Will expand this study to compare prices and quantities to those from IMS.
  - role of discounts may be important....
Data: English prices

Somatropin: Price per mg over time
Omnitrope_Inj 10mg/1.5ml Cart vs. Genotropin_Inj 12mg Cart

brand = orange, biosimilar = blue

Somatropin: Price per mg over time
Omnitrope_Inj 5mg/1.5ml Cart vs. Genotropin_Inj 5.3mg Cart

brand = orange, biosimilar = blue
Data: English quantities

Somatropin: total units over time (1000s)
Omnitrope_Inj 10mg/1.5ml Cart vs. Genotropin_Inj 12mg Cart

Somatropin: total units over time (1000s)
Omnitrope_Inj 5mg/1.5ml Cart vs. Genotropin_Inj 5.3mg Cart
Some observations from Europe

In terms of entry, we see a small number of more meaningful and committed entrants (relative to chemical generics).

Most entrants make significant investments in differentiation (branding) and attempt to establish distribution channels.

By and large, the price reductions arising from biosimilar entry are much smaller than the types of reductions we associate with small-molecule drugs, as expected.

We see variation in both price reduction across biosimilar products and jurisdictions, and variation in penetration across products and jurisdictions.
MIDAS data

Dataset just received from IMS
- 20 countries: Europe plus US, Australia, Canada
- 6 years of annual data on price and quantity
- All biologic products

One European Medicines Agency
- One centralized approval of the biosimilar
- No ability to seek approval at the national level

Many markets, each of which:
- Has national healthcare scheme
- Negotiates price
- Regulates amount of substitutability
- Has different institutions
Empirical strategy

Exploit variation in price and penetration across countries
17 countries, 6 years, 3 product categories

Explain with:
Drug fixed effects
Time since EMA approval
Demographics such as income, age distribution, etc
Variables describing buyer institutions
  Reference pricing and what type
  Financial incentive of buyer (residual claimant?)
  Level of buyer: insurer, hospital, or physician

Is decision-making centralized
Hope the results of that empirical study will illuminate how to take greatest advantage of more limited biosimilar competition.

Method of creating competition matters if price declines and quantity gains vary from almost zero to 30%.

Private sector has incentive to find most effective methods.

Our research is both a chance to influence policy at the FDA concerning entry costs and differentiation, and also the method by which Medicare purchases biologics.
Conclusion

• Competition for biologics without patent protection is critical to controlling future healthcare costs
• Regulatory regime determining entry cost is critical
  Calibration of simple model may help us understand effect of entry regulations on likely market structure
• Biosimilars in Europe have had varied success
  Document facts to show outcomes
  Exploit variation in buying institutions to learn which characteristics of environment are critical
• Policy lessons timely and valuable in US
According to BPCI Act, a biosimilar [351(k)] application must include information showing the product:

- **biosimilar** to reference product (see next slide)
- utilizes **same mechanism(s) of action** for proposed condition(s)—only to the extent known for reference product
- **condition(s) of use** proposed in labeling **previously approved** for reference product
- **same route of administration, dosage form** and **strength** as the reference product.