Manufacturing Barriers to Biosimilar Entry

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Problem(s)

• *Small molecules*: generic competition puts price close to MC when patents expire

• *Biologics*: B/c of challenges, secrecy surrounding manufacturing, no “generic” competition after patent expiry
  – Price decrease of 10-30%?

• Sub-optimal production of basic knowledge regarding biologic products, process
Presentation Roadmap

• Problems, possible solutions
• Significance for larger debates
Caveat: spectrum of molecular complexity

Figure 1
Chemical Structure Comparisons of Select Medications

- Acetaminophen: 151 daltons
- Atorvastatin: 558 daltons
- Filgrastim: 18,880 daltons
- Epoetin alfa: 30,400 daltons
- Rituximab: 145,000 daltons
- Coagulation Factor VIII: 264,400 daltons
Some sales figures

Table I: Combined global prescription sales for the top 50 pharmaceutical companies (excluding generic-drug companies) by molecule type (2009–2014).

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</thead>
<tbody>
<tr>
<td>Small molecule</td>
<td>411</td>
<td>414</td>
<td>415</td>
<td>405</td>
<td>394</td>
<td>394</td>
<td>−4%</td>
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<tr>
<td>Therapeutic protein</td>
<td>65</td>
<td>68</td>
<td>70</td>
<td>72</td>
<td>74</td>
<td>76</td>
<td>17%</td>
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<tr>
<td>Monoclonal antibody</td>
<td>38</td>
<td>43</td>
<td>48</td>
<td>53</td>
<td>58</td>
<td>62</td>
<td>63%</td>
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<tr>
<td>Vaccine</td>
<td>21</td>
<td>22</td>
<td>24</td>
<td>25</td>
<td>27</td>
<td>28</td>
<td>33%</td>
</tr>
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Sources: Datamonitor, PharmaVitae Explorer, January 2010, and company-reported information.
Small molecules vs. Complex biologics

- Generic firm has molecular structure (or can reverse engineer)
- Different manufacturing processes lead to same product
- Showing bioequivalence of copy (Hatch-Waxman) takes $1-2 m

- Even originator doesn’t know precise structure
- Product dependent on process
- Under BPCIA need to show follow-on is “highly similar”
- Follow-on costs under BPCIA (including trials) $100-150 m
Related Scientific Challenges

• Limitations of analytical techniques in proving identity of end product

• Product differences may depend on process differences
  – Including inadvertent changes batch-to-batch (Eprex)
  – FDA makes “comparability” determinations when originator explicitly changes process post-BLA approval
Knowledge Limits By Firm

• Non-originator firms
  – Manufacturing process of originator firm is trade secret

• All firms (at least for complex processes, products)
  – Limited analytics w/r/t end product
  – Correlation between steps of process, product poorly understood
  – Limited incentives for understanding
Limited Incentives

• Originator firms
  – Regulatory lock-in produces suboptimal incentive to investigate manufacturing post-approval
  – Firms’ internal CBA unlikely to push production of basic knowledge/“tech infrastructure”

• Follow-on firms
  – Firms’ internal CBA doesn’t incentivize production of tech infrastructure
Policy Options: Originator Trade Secrets ("OTS")

- Is enablement requirement of composition of matter patent(s) being fulfilled?
  - e.g. Mandel (2006)
  - 21 U.S.C. Section 372(d)
    - Problem is that we care about process at BLA filing/approval time
    - "updating" initial patent with subsequent process changes
  - product-by-process patents (Karshtedt 2011)?
    - Multiple patent apps at different stages?
  - policy question (policy as to disclosure and scope)
Policy Options OTS (2)

• Pushing on patent disclosure may lead to originator’s opting out of patents
  – 12-year exclusivity

• Carrots (e.g. additional regulatory exclusivity for disclosure)
Policy options, basic “tech infrastructure”

Public funding: Arrow plus Pasteur’s quadrant

But expertise in private sector

Public-private: FDA’s “quality by design” product manufacturing initiative
Basic tech infrastructure (2)


  - Industrial: AbbVie, Agilent, Amgen, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Coriolis Pharmaceuticals, Eli Lilly, Genentech, GlaxoSmithKline, Human Genome Sciences-GSK, Janssen (Johnson & Johnson), MedImmune, Novartis, Novavax, PepsiCo, Pfizer, Roche, Sandoz, Thermo Scientific, Waters

  - Regulatory & Standards: FDA, Health Canada, MPA-Sweden, NIBSC-UK, USP, NIBRT-Ireland

  - Academic: University of Birmingham, University of Delaware, Universities of Maryland (Baltimore and College Park) at the Institute for Bioscience and Biotechnology Research (IBBR), University of New Hampshire

  “Precompetitive??” (how much trade secrecy remains)
Larger Themes/Debates

• Role of regulatory lock-in (adaptive regulation?)
• Role of disclosure in justifying patents
• Patents vs. trade secrecy/secrecy
  – Here trade secrecy/secrecy appear to create very significant costs