# Manufacturing Barriers to Biosimilar Entry

W. Nicholson Price II and Arti K. Rai

# Problem(s)

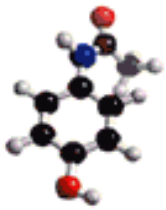
- *Small molecules*: generic competition puts price close to MC when patents expire
- *Biologics*: B/c of challenges, secrecy surrounding manufacturing, no "generic" competition after patent expiry
  - Price decrease of 10-30%?
- Sub-optimal production of basic knowledge regarding biologic products, process

# Presentation Roadmap

- Problems, possible solutions
- Significance for larger debates

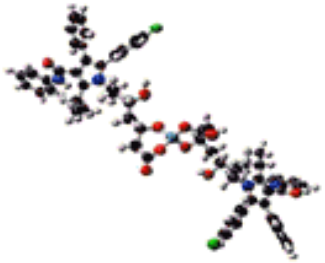
# Caveat: spectrum of molecular complexity

**Chemical Structure Comparisons of Select Medications**



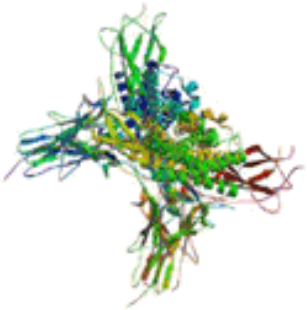
Acetaminophen

151 daltons



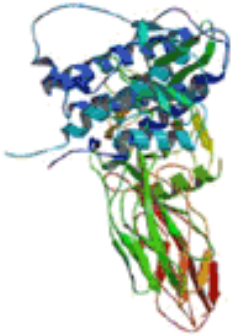
Atorvastatin

558 daltons



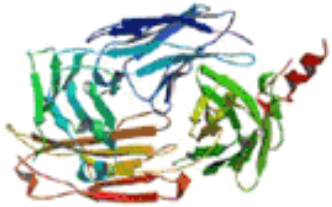
Filgrastim

18,880 daltons



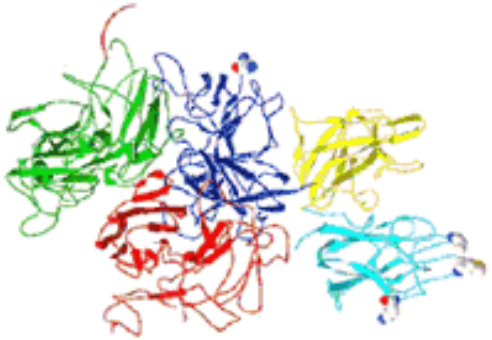
Epoetin alfa

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).**

| | Sales ($ billion) | | | | | | |
|---|---|---|---|---|---|---|---|
| Molecule type | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | Difference in sales between 2009 and 2014 |
| Small molecule | 411 | 414 | 415 | 405 | 394 | 394 | –4% |
| Therapeutic protein | 65 | 68 | 70 | 72 | 74 | 76 | 17% |
| Monoclonal antibody | 38 | 43 | 48 | 53 | 58 | 62 | 63% |
| Vaccine | 21 | 22 | 24 | 25 | 27 | 28 | 33% |

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)

- NIST, http://www.nist.gov/mml/bmd/biomanufacturing.cfm) (*cf.* Sematech)
  - *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