Division of
Pharmacoepidemiology & Pharmacoeconomics
Department of Medicine, Brigham & Women's Hospital, Harvard Medical School

Lessons for Follow-On Biologics from Small Molecule Drugs

Aaron Kesselheim, M.D., J.D., M.P.H.
Assistant Professor, Harvard Medical School
Director, Program On Regulation, Therapeutics, And Law (PORTAL)
February 4, 2014
akesselheim@partners.org

Stakeholder Perspectives

- "[F]rom a technical standpoint there really is no such thing as complete drug equivalence" – Pharmacist
- "Not only has the pharmaceutical industry been successful in maintaining the conviction with many physicians and buyers that not all drugs are alike, but it has even succeeded in persuading them that all products are different" – Drug industry executive
- "I simply say to you that anyone suggesting that one drug firm is as good as another is a fool or naive, or both" – Congressman

Greene, J Hist of Med and Allied Sciences, 2010

Hatch-Waxman Act of 1984

- "Abbreviated" NDA (ANDA)
  - Same active ingredient, route of admin, dosage form, strength → can apply based on bioequivalence data alone
- Data Exclusivity
  - 5 years from date of approval
- Patent certification and litigation
  - Has/will expire, or else "Paragraph IV"
  - Paragraph IV lawsuit and 30-month stay
  - 180-day generic market exclusivity incentive to generic mfrs
- Patent Term Restoration
  - FDA review + ½ time in clinical trials up to max 14 years

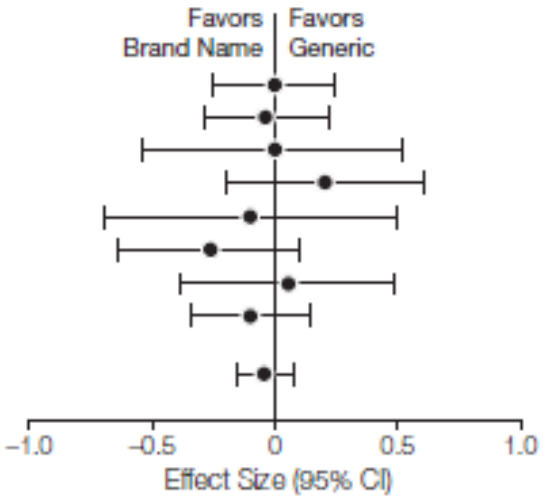
Post-Hatch-Waxman Bioequivalence Rules

- Bioequivalence established on the basis of the maximum serum concentration of the drug (C_{max}), the time until maximum concentration is reached, or the area under a curve defined by serum concentration as a function of time (AUC)
- Bioequivalence required that the 90% CIs for the ratio of brand-to-generic AUC and C_{max} fall within an acceptance interval of 0.80-1.25
- Flexibilities to adapt bioequivalence testing requirements to the clinical situation

Bioequivalence mirrors clinical equivalence

- No evidence that generic small molecule drugs less effective than brand name versions
  - 2008 meta-analysis of CV drugs, 2010 meta-analysis of AEDs
    - Confirmed in well-controlled observational studies

Drug Class	No. Studies	No. Subjects	Effect Size (95% CI)
β-Blockers	6	135	0.00 (–0.24 to 0.25)
Diuretics	10	135	–0.03 (–0.28 to 0.22)
Calcium channel blockers	4	242	0.00 (–0.53 to 0.53)
Antiplatelet agents	2	50	0.21 (–0.19 to 0.61)
ACE inhibitors	1	23	–0.09 (–0.68 to 0.50)
Statins	2	71	–0.25 (–0.62 to 0.12)
α-Blockers	1	43	0.06 (–0.37 to 0.50)
Warfarin	4	138	–0.09 (–0.33 to 0.15)
Overall	30	837	–0.03 (–0.15 to 0.08)

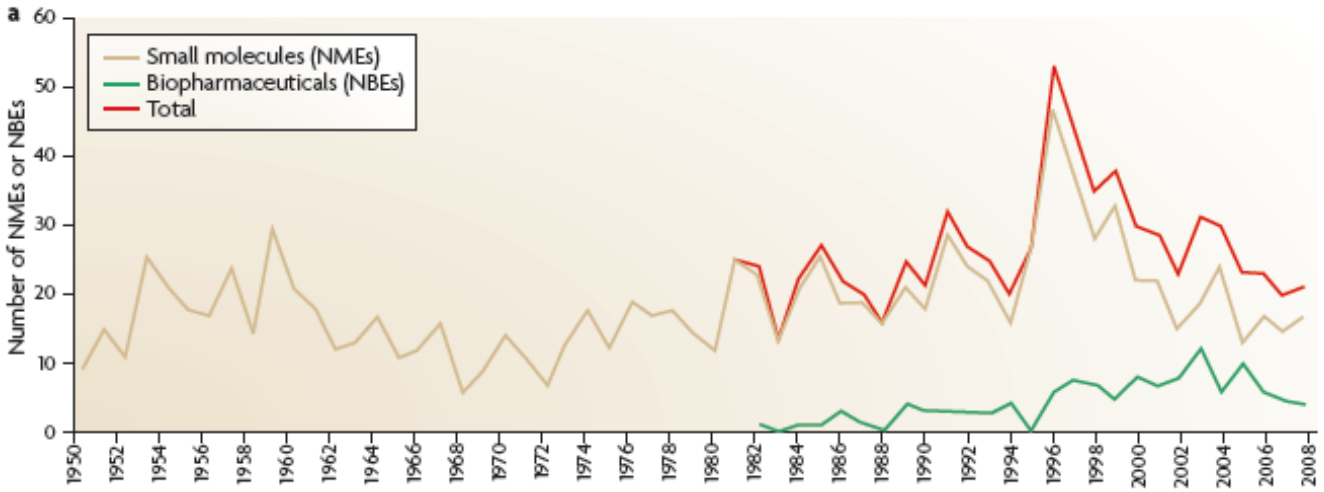


  - 2009 FDA study: avg pharmacodynamic difference of 4%

Kesselheim et al. JAMA, 2008; Kesselheim et al. Drugs, 2010; Davit et al. Ann Pharmacotherapy, 2009

Hatch-Waxman market outcomes

- 1980: 19% Rx for generic drugs; 150 brand-name products with expired patents, no generic alternatives
- 2000: 50% of prescriptions filled with generic drugs
- 2012: 84% of prescriptions filled with generic drugs
- GAO: Save health care system $1 trillion in last 10 yrs



Barriers to generic drug use

- Surveys of physicians and patients show questions about generic drug safety and comparability
  - 2011 survey of physicians: 25% express concern about efficacy, 50% about quality
- Encouraged by brand-name marketing (some explicitly anti-generic), lay media, anecdotal reports in literature
  - Brand-name manufacturers spend $60 billion marketing their products
- Physicians often don't know about drug costs, talk about them with their patients
- 80% use brand-name to refer to multisource drugs

Shrank et al. Ann Pharmacotherapy, 2011; Steinman et al. JGIM, 2007

How have generic small molecules achieved success?

- Drug Product Selection laws allow automatic interchange of A-rated generic products
  - If generic drug proven to be pharmaceutically equivalent and bioequivalent to the brand-name, the generic product gets a therapeutic equivalence code
- Variability:
  - Mandatory vs permissive substitution
  - Patient consent

How have generic small molecules achieved success?

- Evidence: variability in state DPS lead to substantial differences in generic use rates
  - 25% lower substitution rate among Medicaid pts in states with consent requirements; lead to $100M excess spending in Medicaid alone for 3 top-selling medications alone in 1 yr after generic entry
  - Costs per prescription much lower in states without patient consent
  - Lower substitution rates in states with additional pharmacy record-keeping requirements
- Non-A-rated approved generic drugs lead to less savings, use

Carroll et al. Medical Care, 1987; Shrank et al. Health Affairs, 2010

BPCIA

- Two levels of biosimilarity
  - "Highly similar" = no clinically meaningful differences between the biological product and reference product
  - "Interchangeable" = automatic substitution without intervention of prescriber
- 12 years of data exclusivity before authorize any product (+6 mos for drugs approved for pediatric use)
- "Anti-evergreening" provisions, sets biosimilar reimbursement
- Patent dispute resolution process

Lesson #1: Follow-on biologic products scientifically viable

- FDA-approved biologic (or biologic-like) drug products can be used interchangeably
  - Some approved via ANDA process

Generic salmon calcitonin nasal spray

- Polypeptide hormone for osteoporosis, Paget's Disease
  - 32 amino acids, 1 disulfide bond
- In vivo immunogenicity testing required to test to assess potential for anti-calcitonin antibody?
- Clinical trials showing similar clinical effect?
- FDA: Not necessary
  - Allow chemically synthesized generic versions
  - "Structural ordering … during ligand receptor binding is determined primarily by … primary structure"
  - "Impurities…easy to characterize, monitor, and control"

Lee et al., AAPS J, 2011

Generic enoxaparin

- Mixture of oligosaccharides; anticoagulant
- FDA: Approve generic in 2010
  - 1. equivalence of physicochemical properties
  - 2. equivalence of heparin source material and mode of depolymerization
  - 3. equivalence in building blocks
  - 4. equivalence in biological and biochemical assays
  - 5. equivalence in in vivo PD profile
- No additional clinical safety and efficacy data

Lee et al. Nature Biotech, 2013

Lesson #1: Follow-on biologic products scientifically viable

- FDA-approved biologic (or biologic-like) drug products can be used interchangeably
  - Some approved via ANDA process
- European experience (HGH, epo, interferon, insulin)
- Follow the science: interchangeable biologics possible in some cases, not others
  - FDA has expertise available to make decisions, sponsor studies where needed (with appropriate funding)

Lesson #2: Science not enough—name critical

- State DPS laws and naming key to implementation of Hatch-Waxman Act
- Non-interchangeable generic drugs have limited market penetration, higher costs, reduced savings
  - Public remains skeptical about things labeled “generic”
  - Will have to compete against substantial brand-name investment in marketing
  - Help from insurers, academic detailing is possible but impact unclear
- Blanket state anti-substitution carveouts highly problematic for products judged interchangeable

Lesson #3: Creating a viable generic drug market did not reduce brand-name innovation

- 5-year data exclusivity period effective
  - No good evidence that biologic innovation costs substantially more than for small-molecule drugs
  - 12-year period currently in force leads follow-on manufacturers to file regular BLAs
- End of market exclusivity drives innovator companies to develop new, genuinely improved products that will contribute to the next generation of therapies and medical progress

Graham and Higgins, SSRN, 2007;
Carrier, Wisc Law Rev, 2012; Stiglitz, Duke Law J, 2008