The Impact of Hatch Waxman and Antitrust Liability on Incremental Innovation

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Agenda

- What is Incremental Innovation?
- Why Pharma?
- What is Product Hopping
- Review of Hatch Waxman
- What Kind of Product Changes are at Issue
- Notable Product Hopping Cases
- Relevant Law
- Impact on Innovation?

What is Incremental Innovation?

- Improvements on Existing Therapy
  - New Dosage Form
  - New Indication
  - New Therapeutic Regimen
- Cost of Incremental Innovation
  - Clinical Studies
  - Formulation Development
  - Regulatory Requirements
- Return on Investment for Incremental Innovation
  - Patent Exclusivity
  - Regulatory Exclusivity

Examples of Incremental Innovation

- Innovator Drug Valium (diazepam)
  - Rectal Diazepam (Diastat)
  - Intranasal Diazepam
- Innovator Drug Topomax (Topiramate)
  - Extended Release Topiramate – Trokendi XR, Qudexy XR
- Innovator Drug Namenda (Memantine)
  - Extended Release Memantine – Namenda XR
    - Subject to Antitrust Litigation for Product Hop from Namenda to Namenda XR

Why Companies Incrementally Innovate?

- Life-Cycle Management
  - After the reference listed drug is genericized, the economic return on further investment is marginalized
  - Product improvement – What is enough product improvement to withstand antitrust scrutiny
  - New discoveries yielding new patent life
  - Improved patient therapeutic options

Incremental Innovation in a Non-Pharma Context

- Apple is a Premiere Company Employing Incremental Innovation
  - History of Product Improvements that Obsolete Older Products
    - iPhone 1 was a breakthrough product
    - Apple rolls out new version about once a year
    - Goal is life cycle management to sustain maximize company profits

Return on Investment for Incremental Innovation

- Cost of Development Significantly Less than Developing a Novel Drug
- Risks Involved in Development
- Limited Patent Exclusivity
- Limited Protection from Competition
  - Both Supernus and Upsher-Smith developed extended release topiramate products
- Payer Acceptance – Will third party payors cover the new drug?

Patent Law Protects Incremental Innovation

- Patents Provide the Patent Holder the Legal Right to Exclude Others from Practicing the Invention
- Patents Drive Innovation
- Outside of Pharma, Patent Holder Can Exploit the Entire Life of the Patent to Protect Market
  - Patents Provide for a Legal Monopolization

Why Pharma is Different?

- Regulatory barriers to market entry
- Cost of Developing New Drugs
- Pharmaceutical Impact on Healthcare Costs
- Payers Bear A Significant Portion of the Pharmaceutical Costs

Pharmaceutical Pricing

http://www.bhmgnews.com/bh/article_719fc9ea-39a8-11e8-b95b-10604b9f0f84.html

When the new 'pharma bros' show up, prescription prices can go through the roof

By Jared S Hopkins and Andrew Martin / Bloomberg Apr 6, 2018

A pharmacy counter in a Walgreens Boots Alliance store in Elmwood Park, Illinois, on April 5, 2016.
CHRISTOPHER DILTS/BLOOMBERG

Pharmaceutical Pricing- Recent Examples

- Alcortin A gel (Hydrocortisone, Iodoquinol, and Aloe)
  - Price increase from $189 to $7968 per tube
- Indocin Suppositories
  - 30-fold price increase to $2550 per 30 suppositories
- Evzio (Naloxone Auto Injector)
  - Price increase for two injectors from $575 to $4100
- Duexis (Ibuprofen and Famotidine)
  - Price Increase from $140 to $1030 per bottle

What is Product Hopping?

- Product Hopping is a Theory of Antitrust Liability Alleging Attempted Monopolization by the Innovator Pharma Company.
- U.S. Federal Trade Commission's definition of Product Hopping –
  - – "[A] brand-name manufacturer makes minor changes to a drug and, to thwart generic substitution at pharmacies, takes calculated steps to damage the market for the original formulation before generic entry."
- Claims Create Tension Between Patent Law Which Provides a Monopoly Right Under a Patent with Antitrust Laws Which Provide Limits on Monopolization

Innovator Product Hopping

- Branded Product is Facing a Patent Cliff Losing Brand Exclusivity
- Brand Manufacturer Launches a Newer Version of the Drug Before Generic Companies Can Enter the Market with the Generic
- Branded Company Moves Patients to the New Version of the Drug Prior to Generic Entry, Reducing the Number of Rx's for Automatic Substitution Upon Generic Entry

US Regulatory Framework?

- U.S. Regulatory Approach
- Hatch-Waxman was a compromise
  - Ease Entry for Generics While Granting Regulatory Exclusivity to Promote Innovation
  - Abbreviated New Drug Applications (ANDAs) allow generic to piggy-back on innovator's submission by proving pharmacaeutical equivalence
- Provided Multiple Approaches for Generic Entry
  - 505 (j) ANDA
  - 505 (b)(2) NDA
  - Suitability Petition for Changes to Reference Listed Drug

History Behind Hatch-Waxman

- Balance between Innovator's Need For Patent Protection to Foster Innovation and Market Benefits for Generic Entry
  - Benefits for innovators to foster innovation and protect trade secret information.
  - Provided mechanism to enforce patents prior to generic approval and market introduction
- Benefits to Generic by Allowing Reference to Innovator's Safety and Efficacy Data and Providing Incentives to Challenge Innovators' Patents
  - Paragraph IV Patent Challenges

Benefits for Innovators

- Establish exclusivity provisions for NCE's, new indications and supplemental applications
- Eligibility for patent term extension
- Term of Patent Extension
  - Length of regulatory review
    - Half of IND time plus the whole NDA review time
- Limitations on Patent extension
  - Term can't exceed five years
  - Total effective time of the patent can't exceed 14 years
  - Regulatory review time is decreased by any time NDA applicant has not exerted "due diligence" to obtain FDA approval
- Patent application must be filed with USPTO within 60 days of NDA approval

Pharmacoeconomics Aspects

- Pharmacoeconomics incentivize use of generics for lower costs
  - The payers are not the consumers of the products, and therefore have less connection to the brand
  - Insurers often require the use of generic drugs, to reduce costs
- Generic drug takeover since Hatch-Waxman became law in 1984:
  - 1984: 80% of U.S. prescriptions were of brand drugs vs. 20% generic
  - 2016: 10.5% of U.S. prescriptions were of brand drugs vs. 89.5% generic

Benefit for Generic Companies

- Abbreviated Submission Requirement
- Reduced Regulatory Risk and Cost
- Able to Utilize State Pharmacy Generic Substitution Laws
- Enable Generic Companies to Challenge Patents Early and Obtain Generic Exclusivity

Generic Competition

- Generic Products Can Utilize State Pharmacy Substitution Laws
  - Is this the only way generic products can effectively compete?
- Branded Generic Approach
  - Small promotional activities to generate brand awareness
  - Advantage to patients since can limit shifting between generic products
- Role of Managed Care and PBM's
- Incentives for Healthcare Providers

What Kinds of Product Changes Usually Are at Issue?

- Plaintiffs often challenge certain kinds of new product innovations, such as:
  - Immediate release to extended release
  - Capsule to tablet (or other change in form)
  - Changing dosage strengths
  - Scoring of tablets to make the tablets easier to split
- What kinds of market conduct might a plaintiff complain about?
  - "Hard Switch" – withdrawing the older product from the market
  - "Soft Switch" – discontinuing active marketing of the older product, but leaving the product on the market
  - Other measures – Citizen Petitions, withdrawing the New Drug Application, etc.
- Plaintiffs often allege that these changes are timed to avoid the usual impact of generic entry after the expiration of the patent on the older product
  - – This generic entry and subsequent loss of practically all brand sales are known as the "patent cliff"

Notable "Product Hopping" Cases at the Motion-to-Dismiss Stage

- TriCor: Abbott Labs. v. Teva Pharm. USA, Inc.
  - Old version was discontinued
  - Case settled at trial with Abbott paying over $600 million.
- Prilosec-Nexium: Walgreen Co. v. AstraZeneca Pharm. L.P
  - Defendants left the old product on the market, plaintiffs could not allege that defendants interfered with competition
- Suboxone: In re Suboxone Antitrust Litig.
  - Allegations of product withdrawal, coupled with fabricated safety concerns regarding the earlier version, were sufficient to state an antitrust claim
- Asacol: In re Asacol Antitrust Litig.
  - Motion to dismiss granted in part. Because two of the products (Asacol and Asacol HD) were sold contemporaneously, product hop claims as to Asacol HD were dismissed.

Tricor Product Hopping Case

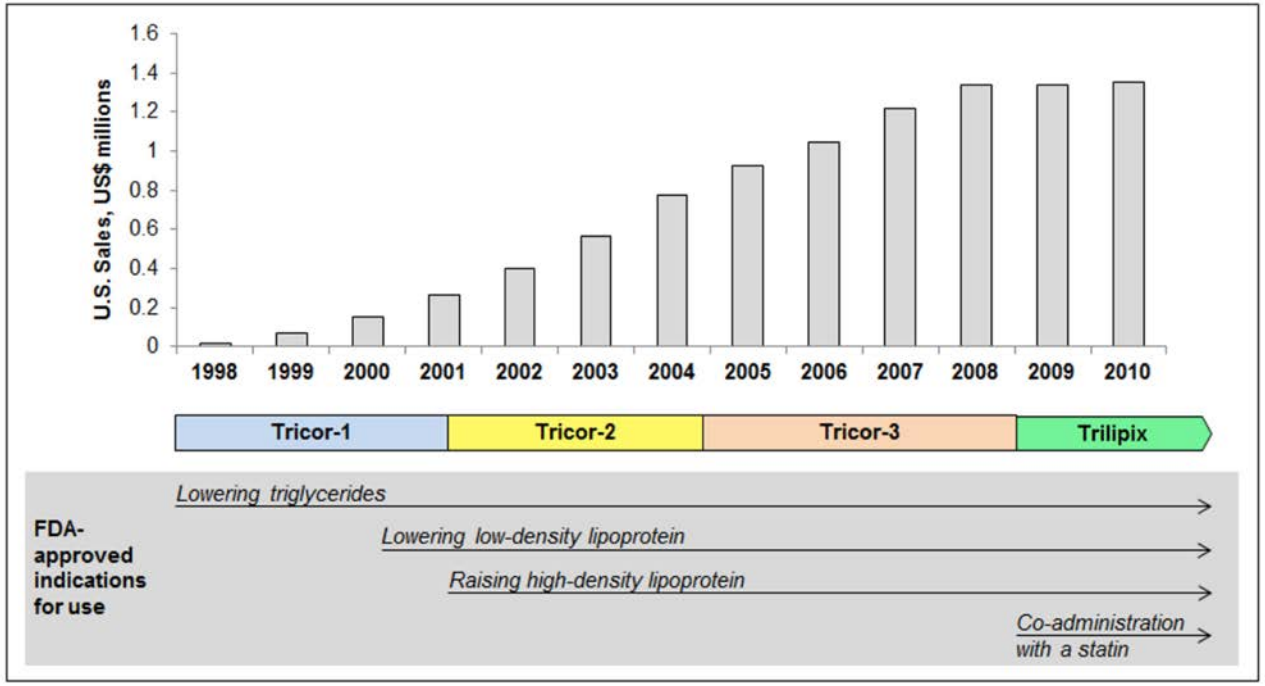
- TriCor: Abbott Labs. v. Teva Pharm. USA, Inc., 432 F. Supp. 2d 408 (D. Del. 2006)

How Abbott's Fenofibrate Franchise Avoided Generic Competition

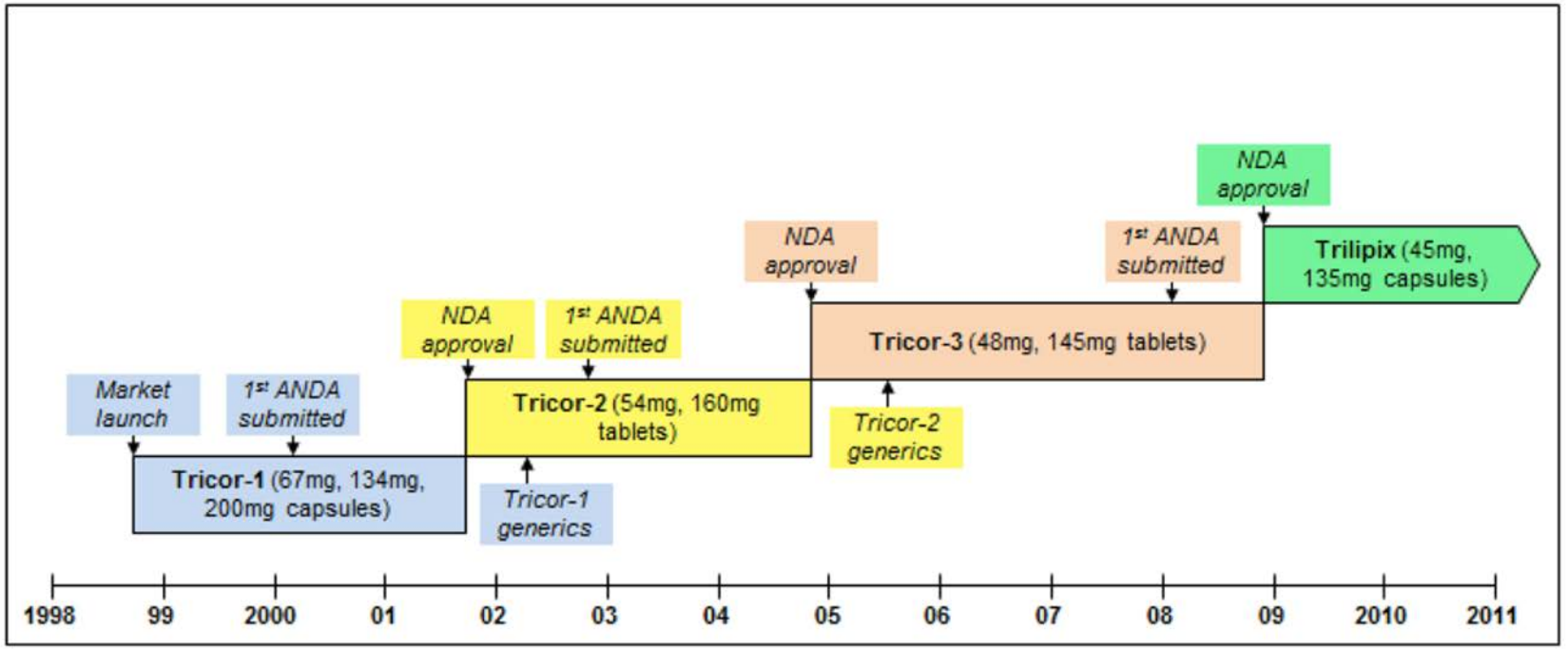
Nicholas S. Downing, AB, Joseph S. Ross, MD, MHS, Cynthia A. Jackevicius, PharmD, MSc, and Harlan M. Krumholz, MD, SM

Arch Intern Med . 2012 May 14; 172(9): 724–730.
doi:10.1001/archinternmed.2012.187

Sales and Indications of Abbott's Fenofibrate Franchise



Evolution of Abbott's Fenofibrate Franchise Relative to Generic Competition



Summary of the Formulations of Fenofibrate

Summary of the formulations of fenofibrate.[13, 19, 22, 23]

Brand name (active ingredient)	Dosing and formulation	Basis of FDA approval	Notable outcomes trials
Tricor-1 (fenofibrate)	67mg, 134mg, 200mg capsules	Clinical trials demonstrating the drug's effect on triglycerides and low-density lipoprotein	Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 2005: Fenofibrate did not reduce rate of cardiovascular events
Tricor-2 (fenofibrate)	54mg, 160mg tablets	Bioequivalence studies that show that Tricor-2 = Tricor-1 Analysis of old Tricor-1 data to support inclusion of high-density lipoprotein-lowering claims in the label No clinical trials	Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, 2010: Fenofibrate did not reduce rate of cardiovascular events
Tricor-3 (fenofibrate)	48mg, 145mg tablets	Bioequivalence studies that show that Tricor-3 = Tricor-1 No clinical trials	None
Trilipix (fenofibric acid)	45mg, 135 mg "delayed release" capsules	Bioequivalence studies that show that Trilipix = Tricor-1 Clinical trials to support the combination therapy indication	None

TriCor Settlement

$250M Settles TriCor Antitrust Class Suit V. Abbott

By **Richard Vanderford**

Law360 (April 24, 2009, 12:00 AM EDT) -- A federal judge has approved a $250 million settlement in the long-running antitrust class action that accused Abbott Laboratories and its French partner Fournier Industrie et Sante of conspiring to block generics makers from breaking into the lucrative market for the high-cholesterol drug TriCor.

Prilosec Antitrust Litigation

December 14, 2006

Pharmacies sue Astra Zeneca for unlawful monopolization of Prilosec/Nexium market

A group of pharmacies led by Walgreen Co. recently filed suit in the U.S. District Court for the District of Columbia, alleging that Astra Zeneca illegally monopolized the market for its proton pump inhibitor drugs Prilosec, Nexium, and their AB-rated generic equivalents, by engaging in a scheme to convert the prescription drug market for Prilosec to Nexium. Proton pump inhibitors are widely used for the treatment of persistent heartburn. In its complaint, the pharmacy group alleges that the scheme was enacted solely for the purpose of impeding generic competition for Prilosec, allowing AZ to continue charging monopoly prices for its proton pump inhibitor drugs free from generic competition.

Prilosec Allegations

The pharmacy group alleges that AZ came up with a scheme to maintain its monopoly by carrying out the following steps designed to convert the prescription market for Prilosec to Nexium:

- Introducing Nexium as a replacement for Prilosec, even though AZ knew that Nexium provided no advantage over Prilosec;
- Engaging in a false and misleading advertising campaign to convince physicians that Nexium is superior to Prilosec, thereby converting Prilosec prescriptions to Nexium prescriptions;
- Withdrawing branded Prilosec from the market and applying for OTC status, which was designed to cause MCOs to stop covering the cost of generic prescription Prilosec; and
- Selling its OTC Prilosec (which was granted 3 year exclusivity in 2003) as a 14 day or less regimen and advising customers to consult their physician if symptoms persisted for more than 14 days; the pharmacy group alleged that this was designed to encourage physicians to prescribe Nexium to OTC Prilosec customers, since MCOs would be unlikely to cover the cost of generic prescription Prilosec.

Product Licensing Antitrust

From *Antitrust Law Daily*, October 21, 2015

Cosmetic surgeon alleges new wrinkle in antitrust claims against Botox maker

By Linda O'Brien, J.D., LL.M.

A cosmetic surgeon sufficiently alleged an injury and causation to pursue antitrust and unfair competition claims against the pharmaceutical manufacturer of the brand drug Botox for allegedly entering into an exclusive license agreement with the foreign manufacturer of a competing neurotoxin product in order to prevent the competitor's impending entry into the U.S. market, the federal district court in Santa Ana, California has decided. Thus, the drug company's motion to dismiss was denied (*Tawfilis v. Allergan, Inc.*, October 20, 2015, Staton, J.).

In-Licensing Product Hopping
Tawfilis v. Allergan

- Allergan Leading Manufacturer and Marketer of Cosmetic Neurotoxins
- Botox Cosmetic is a Lyophilized Product
- Licensed a Aqueous Formulation for Development in the US from Medytox, a Small South Korean Company
- A Group of Dentist Brought a Class Action Lawsuit Alleging the License was Anticompetitive
  - But for the License, Medytox Would Have Brought to the US and Priced at a Discount to Botox Cosmetic
- Is this License Anticompetitive Subject to Antitrust Scrutiny?

Allergan Settlement

Coverage

February 12, 2018

Allergan To Pay $13.5M To End Doctors' Botox Pricing Suit

Allergan Inc. has agreed to pay a class of doctors $13.45 million to settle allegations it inflated the price of Botox by cutting a deal to keep a competing product off the market, according to a proposed settlement filed in California federal court on Friday.

Potential Benefits on Licensing

- Ideal Licensing Partner for Small Company
  - Financial Wherewithal to Develop and Commercialize Product
  - Regulatory Expertise Required to Obtain Marketing Approvals
  - Market Knowledge
  - Prior Success in Therapeutic Area
  - Overall Market Share
  - Sales Coverage
  - Prescribing Physician Relationships

Potential Impact on Subjecting Product Licensing to Antitrust Scrutiny

- Most Ideal Licensing Partners Maybe Off Limits
- Reduce Potential Return on Investment
  - More difficult to maximize opportunity
- Fewer Exit Strategies
  - Most small start up companies do not intend to commercialize products and prefer an exit by license/acquisition
- Make Investment in Start Up Pharma More Challenging

Law Relevant to Product Hopping

- Product Hopping Plaintiffs Often Rely on the Rule of Reason's Balancing Test from Microsoft
  - United States v. Microsoft, 253 F.3d 34, 58-59 (D.C. Cir. 2001):
    - Plaintiff must assert cognizable theory of antitrust harm
    - Plaintiff must show conduct has anticompetitive effect
    - Burden shifts to defendant to offer non-pretextual procompetitive justifications for the conduct
    - Plaintiff must demonstrate that the anticompetitive harm outweighs the procompetitive benefit of the conduct.

Major Antitrust Issues

- Are all Branded Drugs Monopolies?
- Did Product Hopping Harm Competition or Is it Pro-Competitive?
  - How much product improvement is necessary to be pro-competitive?
- Is State Pharmacy Substitution Laws the Only Way Generic Products Can Efficiently Compete in the Market?

Costs Associated with Antitrust Litigation

- Litigation Costs Can Easily Be in Excess of $50M
  - Who Ultimately Pays?
- Uncertain Outcome
  - Drives Settlement of Cases
  - Who Benefits?
- Years to Resolution or Settlement
  - USL Antitrust Case Brought in 2001, Final Settlement 2017
- Takes Focus Off Pharma Business and Innovation

Does Potential Antitrust Litigation Have an Impact on Incremental Innovation?

- Who Are the Winners and Losers?
- What Are the True Costs and Who Bears Those Costs?
- Is Antitrust Liability An Effective Tool for Regulating Innovation?