Pharmaceutical Antitrust Law

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Final Papers – Any questions? Schedule time during office hours!
- Abby also available for meetings or review of drafts
- Class on November 1st is NOT rescheduled (for now)

Upcoming guest speakers:
- October 21st: Ayana Jordan, MD, PhD
- October 23rd: Jessie Gaeta, MD

Current Events in Drug Law
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(1) Price Fixing Antitrust Litigation
(2) Patent Thickets
(3) Pay-for-Delay
(4) Exclusive Dealing/Bundling
(5) Product Hopping
(6) FDA Citizen Petitions
(7) Denial of Samples/REMS
(1a) Insulin Price Fixing

Table 2: Insulin Available in the United States

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Active</th>
<th>Brand Name</th>
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Why has the price of Humalog insulin gone up 700% in 20 years? It’s simple. The drug industry’s greed.

The list price of Humalog insulin keeps going up.

Since 2000, there have been more than two dozen price increases on a drug that is widely used. Adjusted for inflation, the current price is 700% higher than it was 20 years ago.

Rising Insulin Prices
(1a) Insulin Price Fixing

- Racketeer Influenced and Corrupt Organizations Act (RICO)
  - Definition of racketeering typically thought of as organized crimes or crime syndicates
  - RICO broadened that definition, includes 35 enumerated forms of racketeering
  - Current case alleges an “organized scheme” between the 3 largest insulin manufacturers (Novo Nordisk, Sanofi, and Eli Lilly) and the 3 largest pharmacy benefit managers (ExpressScripts, CVS Health, and OptumRx)

- Case alleges that insulin pricing is an “arms race” for manufacturers seeking to win over PBMs (that collect a percentage of the discount they pass on to clients)
  - Increasing list price is a way for manufacturers to offer better payment to the PBM (entity that often has significant sway in terms of “preferred” formulary/insurance coverage)
  - Greater differential between list price and discount price – PBM makes more $$$

(1a) Insulin Price Fixing

- Publicly reported benchmark (or list) price has risen over 150% in 5 years
- List prices differ from the “lower, real price manufacturers offer to certain bulk distributors”
- Increased list prices often translate into increased costs to consumers (especially when patients pay coinsurance instead of copayment)
(1b) Generic Drug Price Fixing

- Horizontal Conspiracy to Allocate Markets and Fix Prices for Multiple Generic Drugs in Violation of Section 1 of the Sherman Act
  - The Overarching Conspiracy: Customer And Market Allocation Agreements To Maintain Market Share And Avoid Price Erosion ("Fair Share")
  - Taking The Overarching Conspiracy To A New Level: Price Fixing (2012 – 2015)
  - Competitors Become "High Quality" After Successfully Colluding With Teva
  - "Quality Competitors" Collude With Each Other As Well (Not Just With Teva)

(1b) Generic Drug Price Fixing

- A Commitment To The Overarching Conspiracy Was Instrumental To The Success Of The Price Fixing Agreements
- "Quality Competitor" Rankings Relate To Price Increases, But Even "Low Quality" Competitors Collude With The Overarching Conspiracy
- Teva Profitability Increases Dramatically As A Result Of Price Increases
- Teva and Its Executives Knowingly Violated The Antitrust Laws
- Price Increases Slow Dramatically After Government Investigations Commence

(1b) Generic Drug Price Fixing

- Interactions and Communications Occurred Over:
  - Trade Association and Customer Conferences
  - Industry Dinners and Private Meetings
- The Overarching Conspiracy: “Playing Nice in the Sandbox”
  - "when necessary, this larger understanding was reinforced through phone calls and text messages between the Defendants to discuss ‘fair share’ and the desire to maintain or raise prices with respect to specific drugs"

(1b) Generic Drug Price Fixing

- Table 1

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(1b) Generic Drug Price Fixing

- Table 2

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(1) Price Fixing Antitrust Litigation
(2) Patent Thickets
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(2) Patent Thickets
A study of the HIV drugs ritonavir and lopinavir found patents covering:
• Related chemical structures and compositions or formulations (81)
• Manufacturing methods and processes (68)
• Methods of disease treatment (31)
• Other more general patents (28)

Amin T, Kesselheim AS. Secondary patenting of branded pharmaceuticals: a case study of how patents on two HIV drugs could be extended for decades. Health Affairs 2012;31(10):2286‐2294.

Patent Thickets
Humira (adalimumab), the #1 grossing drug in the world (> $20b in annual sales), has over 110 unexpired patents, including:
• 14 on its formulation
• 24 on methods of manufacture
• 22 on methods of treating particular diseases, and
• 15 on other aspects of its technology

http://www.biopharmalaw.com/blog/humira‐how‐to‐develop‐a‐strong‐patent‐portfolio‐in‐the‐aia‐and‐bpcia‐era

Patent Thickets and Antitrust
• In April 2019, litigation against AbbVie for anticompetitive conduct:
  • Statement of firm representing plaintiffs: “Had AbbVie not engaged in anticompetitive conduct, the plaintiffs would have been able to purchase Humira biosimilars in the U.S. as early as January 1, 2017, the expiration of Humira’s primary patent, at significantly lower prices.”
  • Plaintiffs also point to a “concerted effort” in settlement agreements with 8 manufacturers to delay biosimilar entry in the U.S. until at least 2023 while allowing biosimilars to enter in Europe in 2019
• Settlement agreements represent an “anticompetitive scheme to restrain competition in the market for Humira.”

(3) Pay For Delay
• Means of settling litigation (often patent infringement)
  • In lieu of deciding case on its merits (which could invalidate patents or parts of patents but is costly/time consuming)
  • Brand and generic manufacturer agree to date of generic entry, licensing/royalties, etc.
• Increasingly scrutinized by FTC/DOJ
• e.g., Settlement between AbbVie/Amyent re: Humira and Amjevita (approved 9/2016, will not be launched until 1/2023)
(3) “Pay-for-Delay” or Reverse Payment

- Used to literally be “pay-for-delay”: brand manufacturer would PAY the generic manufacturer to DELAY market entry and competition
- Decision allows FTC to scrutinize settlement agreements between pharmaceutical manufacturers

Solving the 180-day Bottleneck

- Expand the universe of parties eligible for 180-day exclusivity
  - Fair and Immediate Release (FAIR) of Generic Drugs Act expands definition of “first applicants” to include generics:
    - That obtain judicial invalidity/noninfringement decisions
    - That are not sued for infringement
  - Arguably, 180-day incentive is not needed
  - The prospect of shared 180-day exclusivity does not stop first-filing challenges by multiple generics
  - The presence of authorized generics does not reduce challenges, even in small markets
- Addresses concern raised in *FTC v. Actavis*
  - At oral argument in *FTC v. Actavis*, Justice Scalia stated that “Hatch-Waxman made a mistake;”
  - Justice Kagan lamented the Act’s “glitch” was “that the 180 days goes to the first filer” and that once the filer “is bought off, nobody else has the incentive” to challenge patents

Redefining “Payment”

- FTC has recently argued that the term “pay-for-delay” is obsolete
- Protecting Consumer Access to Generic Drugs Act of 2019:
  - Creates framework of illegality applying when generic receives “anything of value” (including exclusive license) and delays “research . . . , development, manufacturing, marketing, or sales”
  - By defining illegality, the bill helps FTC prove cases in court and recover a penalty
  - Parties still allowed to settle cases, but based on the patent, not a payment
  - The bill would address errors like *FTC v. AbbVie* (3d Cir.)
    - Brand provided generic with its AndroGel testosterone product at price “well below what is customary” (unrelated generic services)
    - The court, despite recognizing deal’s “large value,” concluded it was not a reverse payment

(3) “Pay-for-Delay” or Reverse Payment

- The first generic manufacturer to challenge brand manufacturer patents as invalid obtains 180 days of market “duopoly”
  - There can be more than one award (“shared exclusivity”)
- Arguably, the 180-day exclusivity period has been twisted from an incentive to invalidate patents to a bottleneck limiting generic entry
  - Brand-name manufacturer generally counters with infringement litigation, automatic 30-month stay for litigation to complete.
  - By settling patent disputes with the first-filing generic, the brand manufacturer delays entry by all generics
  - The 180-day period only begins when the first generic enters the market

Relationship to *FTC v. Actavis*

- Two amendments to the Protecting Consumer Access to Generic Drugs Act would make clear that courts cannot undermine landmark *FTC v. Actavis* decision:
  - Generic entry before end of patent term is not automatically procompetitive
    - E.D. Pa. court in *AbbVie* and Administrative Law Judge in *Impax* assumed pre-expiration entry procompetitive
  - Risk aversion is not a legitimate procompetitive justification
    - Third Circuit in *Wellbutrin* relied on risk aversion to dismiss argument that size of payment reflects patent weakness (even though this had been rejected by the Supreme Court as defense)
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(4a) Exclusive Dealing

An exclusive dealing arrangement is an agreement requiring a buyer to purchase all needed goods or services from one seller/manufacturer.

Infliximab (Remicade, Johnson & Johnson) & Inflectra (Pfizer)
- J&J developed a “Biosimilar Readiness Plan” aimed at thwarting Inflectra and other biosimilars from gaining market share
- 90% of all accounts using Remicade purchased no Inflectra
- Inflectra peaked at 4% of market share
- Meanwhile, J&J continued to increase the price of Remicade

(4b) Bundling

Bundling involves discounts a manufacturer offers to purchasers buying several products in its portfolio and can result in prices competitors struggle to match.

Cyclosporine (Restasis, Allergan) and Lifitegrast (Xiidra, Shire)
- Allergan sold Restasis to Medicare Part D plans with 3 other glaucoma drugs, and offered significant discounts for purchasing all 4
- Discount was so significant that Shire alleged it could not match the price for Restasis, even if it offered Xiidra FOR FREE
- Result: Restasis controls 90% of Medicare Part D marketplace

(4) Exclusive Dealing and Bundling

- Not necessarily antitrust violations, but warrant greater scrutiny when resulting in preservation of a monopoly (or near-monopoly)
  - May result in exclusion of rival from market access, market withdrawal by competitor, and reinstatement of monopoly (or near-monopoly) pricing
(5) Product Hopping

- Product-hopping is a mechanism by which manufacturers attempt to extend market exclusivity for lucrative drugs for which market exclusivity is set to expire
  - Often a part of “product lifecycle management” strategies developed by manufacturers over time
  - Manufacturers modify aspects of their drugs, obtain new patents, and seek FDA approval of these modifications in order to prolong exclusivity of lucrative brand-name drugs

- When coupled with actions that encourage prescribing of the modified brand-name product instead of the original product, the introduction of the modified product may make no economic sense other than harming the generic

Examples:
- Doryx (doxycycline): capsule to tablet to scored tablet
- Namenda (memantine): instant release to extended release
- Advair (fluticasone/salmeterol): Diskus to HFA inhaler

(6) FDA Citizen Petitions

- Section 505(q), allows any entity (individual, company, etc.) to ask the FDA to take a specific action
  - Many examples of brand manufacturers submitting citizen petitions against pending generic applicants, asking FDA to reject ANDAs
  - From 2011-2015 (124 total petitions):
    - 92% were filed by brand firms
    - Only 8% of petitions were granted
    - 39% of petitions were filed within 6 months of expiration of patent or regulatory exclusivity

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(7a) Restricted Distribution Networks

- Turing Pharmaceuticals acquired marketing rights to pyrimethamine (Daraprim).
  - Decades-old drug, used to treat toxoplasmosis (which commonly occurs in the setting of end-stage HIV infection)
  - Under CEO Martin Shkreli, Turing promptly raised the price by over 5000%, from $13.50 a pill to $750 a pill

(7b) Denial of Samples for Testing

- Completing bioequivalence studies requires generic manufacturers to obtain samples of the brand-name Reference Listed Drug
  - Direct contact with brand-name manufacturer or working with wholesaler or other middleman
  - Transactions completed without a prescription, supplies shipped in bulk form suitable for clinical testing
(7b) Denial of Samples for Testing

- Generic manufacturers need brand manufacturers to provide samples to conduct bioequivalence studies for ANDA approval; brands have denied them
  - FDA received 150 inquiries from generics unable to obtain samples
  - Delays reported to cost $5+ billion/year in lost savings from generic entry
  - FDA has a new "name and shame" list of companies that deny samples

(7b) Denial of Samples for Testing

- Creating and Restoring Equal Access to Equivalent Samples Act (CREATES) of 2019
  - Would allow targeted lawsuits by generic firms to obtain samples from branded firms
  - Would provide assurances for safety, limitations for liability, and remedies in case of abuse
  - Congressional Budget Office estimates savings of $3.8 billion over 10 years
- Fair Access for Safe and Timely (FAST) Generics Act of 2019
  - HHS Secretary can require access to samples as condition of approval/licensing

(7c) Risk Evaluation and Mitigation Strategies (REMS)

- Created by FDAAA in 2007
- Generics required to share a single REMS with brand manufacturer
  - Companies have slow-walked negotiations to create single, shared REMS (sometimes for years)
  - FDA has authority to issue "generics are safe" letters related to drugs with REMS, but they have been largely ineffective at compelling sharing of samples
  - Sample denials violate legislative provision that brands not use REMS to "block or delay" generics
- FAST Generics Act of 2019: Would provide that if brand and generic firm cannot agree to a single, shared REMS in 120 days, the shared REMS requirement is waived
- CREATES Act of 2019: Would provide a solution to single, shared REMS problem by permitting development of a "different, comparable" REMS for the generic

(7c) Patenting REMS

- FDAAA explicitly permits patenting of REMS
- Brand manufacturer describes REMS in its product label, but the generic is statutorily required to have an identical label
- Patents on REMS programs thus put generic manufacturer between FDA law (don't alter the label!) and patent law (don't infringe the patent!)
- Orange Book Transparency Act of 2019: proposed amendment to the bill would prohibit listing of REMS patents in Orange Book

Any questions?

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TA: Abby Fletes, fletes.a@husky.neu.edu