# Follow-on Biologics: Working with the Federal Trade Commission

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# Follow-on Biologics

## BPCIA Refresher, FDA Developments, and Major Takeaways from the FTC's Biologics Workshop

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# Agenda

- BPCIA Refresher
- FDA Developments - Purple Book, FDA Review of Applications, Draft Guidance, Abbott Petition
- The Naming Issue
- State Substitution Laws

# Biologics Price Competition and Innovation Act of 2009

- BPCIA passed as Title VII, Subtitle A of the Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119, §§ 7001-03.
- Signed into law on March 23, 2010.
- Effects a large and rapidly growing market

# BPCIA Refresher

- Key Provisions
  - Approval pathway
  - Data requirements
  - Interchangeability
  - FDA process
  - Exclusivity
  - Drug to Biologics transition
  - Patent issues

# BPCIA Refresher

- Amends the PHS Act by adding:
  - Section 351(k) – licensure requirements for biologics as either: Biosimilar or Interchangeable
  - Section 351(l) – patent infringement disputes

# BPCIA Refresher

- "Biosimilar" defined:
  - Highly similar to the reference product notwithstanding minor differences in clinically inactive components.
  - No clinically meaningful differences from reference in terms of safety, purity, and potency.

# BPCIA Refresher

- FDA may approve as interchangeable if:
  - Biosimilar
  - Expected to produce the same clinical result in any given patient
  - If administered more than once, risk of alternating or switching is not greater than using reference alone
- "Interchangeable" defined:
  - "may be substituted for the reference product without the intervention of the health care provider who prescribed the product"

# FDA Developments - “Purple” Book for Biosimilars

- OND Director John Jenkins stated in December that FDA intends to develop an Orange Book like tool for biologics.
- Originally the “Purple Book” but the name has been taken.

# Biosimilar Applications at FDA

- 36 biosimilars are in the “product development stage” as of mid-December.
- FDA will not disclose whether any 351(k) applications have been received. But in November it changed its rhetoric from “we have received no applications” to “none have been approved.”
- FDA has acknowledged that numerous Type 4 meetings (format and content) have occurred.

# The FDA Draft Guidances

- Three of them released in 2012 – scientific considerations in demonstrating biosimilarity, quality considerations in demonstrating biosimilarity and Q and A regarding implementation (biosimilarity v. interchangeability, exclusivity and definition of a biological product).
- FDA intends to release final versions in 2014.

# Abbott Humira Petition

- Abbott April 2, 2012 citizen petition (Docket No. FDA-2012-P-0317).
- Abbott argues that applying the BPCIA to biosimilar applications that reference a BLA submitted to FDA before BPCIA enactment would constitute a “taking” that requires just compensation under the Fifth Amendment.

# Abbott Humira Petition

- Abbott's basic argument is that:
  - (1) the Fifth Amendment prohibits taking property without just compensation;
  - (2) trade secrets are property for Fifth Amendment purposes;
  - (3) information provided to FDA in support of a BLA is trade secret information;
  - (4) applying the BPCIA to pre-BPCIA BLAs "takes" those trade secrets because it allows a second company to free-ride on the RP sponsor's trade secrets;
  - (5) the BPCIA thus should only be applied to BLAs submitted after the BPCIA's enactment.

# Abbott Humira Petition

- Abbott's claims find support in the Supreme Court's decision in Ruckelshaus v. Monsanto Co., 467 U.S. 986 (1984).
  - Trade secrets presented to a federal agency can be property for Fifth Amendment purposes.
  - The manner in which an agency uses trade secrets can constitute a taking.

# FTC Workshop of Tuesday, February 4, 2013

- Two Main Topics
  - Names of Biologics
  - State Substitution Laws
- Twenty outside speakers plus numerous FTC participants including Chairman Ramirez
- FDA conspicuously absent
- FTC concerns apparent but ability to influence questionable

# The Naming Question . . . .

- Must each biosimilar have a unique name in order for patients and physicians to easily distinguish between medicines and to track and trace adverse events for such products?

# History

- The “naming issue” has been around since well before the May 23, 2010 enactment of the BPCIA.
- In an October 2006 Policy Position submitted to the WHO, several organizations, including PhRMA and BIO, recommended distinct INNs for each biotechnology-derived therapeutic protein produced by different manufacturers.
  - To “accommodate the acknowledged complexity of protein medicinal products and… facilitate safe prescription and dispensing of medicines and preserve patient safety.”
- The BPCIA does not address biosimilar product naming.
- Because of the projected size of the U.S. biosimilars market, the “naming issue” has become a heated debate – letter from Congress, citizen petition.

# Biologics Naming: INN/USAN

- INN and USAN are working toward alignment; negotiations are aimed at achieving consensus.
- They both use similar approaches for naming biologics
  - Defining characteristics for biopolymers is the primary sequence
  - Biopolymers (proteins) with different glycosylation pattern are differentiated using a Greek suffix
  - Further elements of the name can include numbers (Interferon Alfa – 2a)
- At a recent INN meeting (April 15-18, 2013), a consensus emerged to develop a naming convention for biosimilars.
- At a public INN meeting (October 2013), INN suggested a classification system for biosimilars, separate from the INN.

# Biosimilar Product Maker Position

- Each biological product is clearly identified by its brand name.
- The INN identifies the active substance and is not suitable for product identification.
- Different INNs for biosimilars would confuse physicians.
- Implied inferiority
- The current naming system for biologics works well and should not be dismantled.
- Additional means of identification such as NDC numbers, lot numbers and manufacturer names suffice for pharmacovigilance purposes.

# The Reference Product Maker Position

- Distinct nonproprietary names are based on scientific principles that reflect the complexity of both the molecules and the manufacturing processes.
- Distinct names justified by global experience and necessary for tracking adverse events.
- NDC and lot numbers are not adequate for pharmacovigilance.
- Policy measures that are transparent, scientifically consistent and that encourage accountability will develop trust in biosimilars.

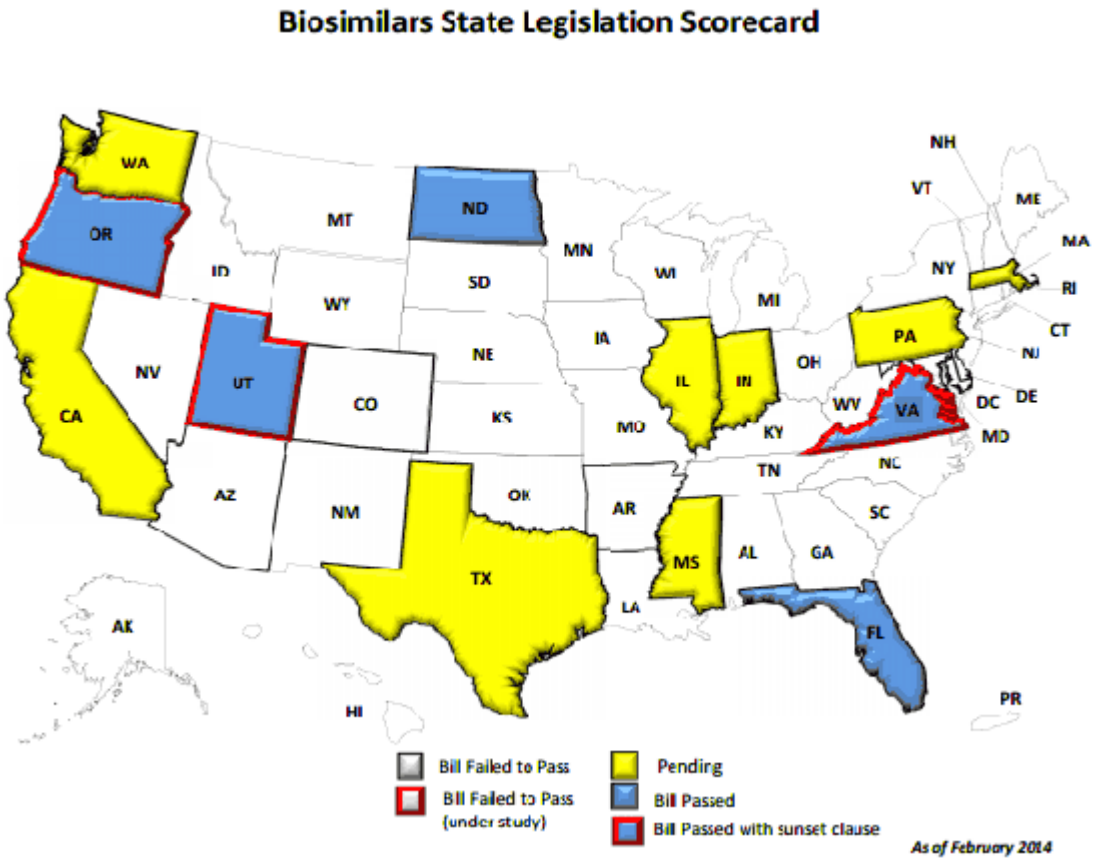
# State Substitution Laws

- Although FDA has not approved a biosimilar application – let alone define interchangeability – many states are considering and passing legislation governing the substitution of interchangeable biosimilar biological products.

# 2013 Biosimilar Legislation Scorecard

- Bills introduces in 18 states
- Rejected in 10 states – AZ, AR, CA (vetoed), CO, DE, IN, MD, MS, TX, WA.
- Enacted in 5 states – FL, ND, OR, UT, VA.
- Carried over in 3 states – IL, MA, PA.

# Biosimilars State Legislation Scorecard



# Typical State Legislation Requirements

- Substitution should occur only when FDA has designated a biologic product as interchangeable.
- The patient should be notified of the substitution.
- The prescribing physician should be notified of the substitution.
- The pharmacist and the physician should keep records of the substitution.

# State Substitution Law Concerns

- Premature
- Confusion
- Undermines Public Confidence

# Development in Washington State

- Three companies developing biosimilars – Actavis, Sandoz and Hospira – have come out in support of a substitution bill.
- Bill requires substitution unless the patient or prescriber specifies the brand name drug.
- Bill requires pharmacists to record the name and manufacture of the product in an interoperable health record within ten days or, otherwise communicate to the practitioner.

# Development in Washington State

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# Follow-on Biologics

## *Sandoz v. Amgen*: rehearsal for the dance

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# Biosimilars patent dispute resolution

- The BPCIA created an elaborate patent dispute resolution mechanism for biosimilars
  - modeled in part on Hatch-Waxman patent dispute mechanism, but with significant differences driven by -
    - criticality of the manufacturing process to the identity and characterization of the reference product *and* the follow-on biologic
    - lack of an Orange Book analog ("*Purple Book*")

# Biosimilars patent dispute resolution

- The BPCIA created an elaborate patent dispute resolution mechanism for biosimilars
  - mechanism is complex
    - several rounds of confidential information exchange directly between reference product sponsor and biosimilar applicant
    - two separate waves of litigation
    - strict timing and sequencing requirements

# Biosimilars patent dispute resolution

- The mechanism is *specific to* 351(k) biosimilar applications
- It is *not applicable* to follow-on biologics approved under full BLA
  - *e.g.*, Teva's G-CSF follow-on, GRANIX (tbo-filgrastim)

# *Sandoz v. Amgen*

- provides the first (*tangential*) look at the biosimilar patent dispute resolution mechanism
  - ***explicitly*** speaks only to interplay with DJ actions
  - ***implicitly*** raises other issues
    - selection of approval route: 351(k) *vs.* full BLA
    - use of post-grant challenges in USPTO
      - inter partes review (IPR)
      - post grant review (PGR)
      - ex parte reexam

# *Sandoz v. Amgen*

- Background
  - *Sandoz: "Just as its patent position [on etanercept] is set to expire, Amgen obtains two submarine patents"*
    - earliest claimed priority date, September 12, 1989
    - pre-GATT
      - unpublished before issuance
      - term 17 years from issuance
    - expire November 22, 2028 & April 24, 2029
    - exclusively licensed from Roche in 2005

# *Sandoz v. Amgen*

- Litigation
  - **June 24, 2013** – **Sandoz** complaint (ND CA) for declaratory judgment of invalidity and unenforceability
  - **August 16, 2013** – **Amgen** motion under 12(b)(1) to dismiss for lack of subject matter jurisdiction, or for court to decline to exercise DJ jurisdiction
  - **Sep 23 & Oct 15, 2013** – **Sandoz** Reply, Sur-reply
  - **November 12, 2013** – **Order** granting Amgen motion, denying leave to amend complaint
  - **Dec 12, 2013** – **Sandoz** notice of appeal to Fed Cir

# *Sandoz v. Amgen*

- Order (Chesney, J.) – motion to dismiss granted
  - Basis 1: DJ jurisdiction constrained by biosimilar dispute mechanism
    - the DJ statute explicitly states that there are limitations as to DJ "actions brought with respect to drug patents" under "section 351 of the Public Health Service Act." 28 U.S.C. § 2201(b)
    - Sandoz had not yet filed a 351(k) application
    - Court: "[N]either a reference product sponsor, such as Amgen, nor an applicant, such as Sandoz, may file a lawsuit unless and until they have engaged in a series of statutorily-mandated exchanges of information. See 42 U.S.C. §§ 262(l)(2)-(6)."
      - rejects Sandoz's "notice of commercial marketing" argument

# *Sandoz v. Amgen*

- First basis for decision *not relevant* if full BLA route
  - the patent dispute resolution procedures are applicable ***only*** to 351(k) biosimilars
    - **an aside**: until Sandoz's Opposition brief, there was no evidence in the record that Sandoz was contemplating a 351(k) application rather than full BLA
    - **query:** should the possibility that DJ jurisdiction might be achieved earlier with a full BLA now figure into the choice of approval route?

# *Sandoz v. Amgen*

- Order (Chesney, J.)
  - **Basis 2:** as a factual matter, a cognizable case or controversy does not exist
    - **Court:** Sandoz has not, at this time, established a "real and immediate injury or threat of future injury that is caused by the defendants." No explicit threat of suit by Amgen, and Amgen is "not in a position to consider the propriety of such action until after Sandoz has 'prepared an [application] for approval to launch a product in the U.S.'"
    - **Court: "**Sandoz's allegation that it intends in the future to file an application with the FDA is insufficient to create a case or controversy."

# *Sandoz v. Amgen*

- Was DJ the best or only option?
  - What about inter partes review (IPR)?
    - generally, a favorable forum for challengers
      - lower burden (preponderance)
      - broader claim scope (broadest reasonable interpretation)
      - fast adjudication (statutory – 12 months)
      - sophisticated audience (APJs)
    - precedent now established on small molecule side
      - Apotex and Ranbaxy among current petitioners

# *Sandoz v. Amgen*

- Was DJ the best or only option?
  - but, IPR is limited to patents and printed publications
    - and Amgen-licensed patents have earliest priority date of 1989, an atypical fact pattern for the late-expiring patents protecting reference product
      - more typically, the later-expiring patents are later-filed, and the first generation patent and intervening scientific/medical literature are available as prior art
    - §102(g) prior invention by Immunex likely not cognizable
      - not cognizable in reexam
      - and evidence uniquely in hands of Amgen, requiring discovery

# *Sandoz v. Amgen*

- Was DJ the best or only option?
  - *and possibly*, obviousness-type double patenting
    - but it is currently unknown whether double patenting will be cognizable basis for IPR
      - availability in ex parte and inter partes reexam proceedings is a judicial construct
      - and statutory language and legislative history differs
    - but even if double patenting were cognizable in IPR, the Amgen-licensed patents have different ownership and different inventorship from Amgen's (Immunex's) earlier-issued etanercept patents

# *Sandoz v. Amgen*

- Was DJ the best or only option?
  - and IPR creates estoppel as to defenses available in later litigation
    - precludes in later litigation "any ground that the petitioner raised *or reasonably could have raised* during that inter partes review"
    - legislative history suggests that scope of "reasonably could have raised" should lie somewhere between actual knowledge and findable only in a "scorched earth" search
    - an aside: for inter partes reexam, PTO is taking the view that the analogous "could have raised" estoppel is limited to actual knowledge. This has not been adjudicated, and the statutory language and legislative history differs as between IPX and IPR

# *Sandoz v. Amgen*

- Was DJ the best or only option?
  - regardless of scope of "*could have raised*" estoppel, Sandoz would have retained
    - unenforceability defenses
      - prosecution laches
      - inequitable conduct
    - 112 defenses
      - written description
      - enablement
    - §102(g) prior invention (by Immunex) defense

# *Sandoz v. Amgen*

- Was DJ the best or only option?
  - IPR now likely barred
    - **AIA 35 U.S.C. §315(a)** An inter partes review may not be instituted if, before the date on which the petition for such a review is filed, the petitioner or real party in interest filed a civil [DJ] action challenging the validity of a claim of the patent.

      - Sandoz would need to argue successfully that dismissal of DJ action for lack of subject matter jurisdiction renders DJ action constructively ***not*** "filed" (void *ab initio*) – an issue of first impression

# *Sandoz v. Amgen*

- Was DJ the best or only option?
  - What about post grant review (PGR)?
    - only available for AIA first-to-file patents, and Amgen's patents are not only *pre-AIA*, but *pre-GATT*
    - as to AIA patents, PGR will be available based on "on any ground specified in [35 USC §§ 100 - 212] as a condition for patentability," except failure to disclose the best mode
    - scope of estoppel as to grounds that can be brought in later litigation will be commensurately greater

# *Sandoz v. Amgen*

- Was DJ the best or only option?
  - What about *ex parte* reexam?
    - although can be brought anonymously and carries no estoppel, terribly unfavorable forum for third party requester

# *Sandoz v. Amgen*

- How is IPR likely to figure into biosimilar patent strategy?
  - IPR should be most effective against the patents having the latest effective filing dates
    - these are the patents that are subject to the largest universe of patents and printed publication prior art
  - IPR invalidation of patents with the latest expiries should have the greatest effect on the biosimilar applicant's NPV calculations
    - these are the patents that establish earliest possible date of entry

# *Sandoz v. Amgen*

- How is IPR likely to figure into biosimilar patent strategy?
  - IPR should offer greatest opportunity and benefit with respect to patents having both latest effective filing dates and latest expiries
  - if double patenting is cognizable in IPR, patents having latest effective filing dates, latest expiries, ***and*** latest issue date

# Follow-on Biologics

## FTC Expertise, Enforcement, and Competition Advocacy

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# Outline

- FTC Expertise
- Enforcement
- Competition Advocacy
- Ways the FTC Can Help in the FOB Debate
- FTC Analysis of Patient Safety Claims

# FTC Expertise


- Economics
  - FTC is one of the largest employers of PhD economists in the world
  - Focus on pricing and price competition
  - Knowledge of price competition in small molecule drugs
- Science
  - Has relied on FDA when assessing innovation in small molecule drugs
- Intellectual property
  - Relatively small number of IP attorneys

# Outline

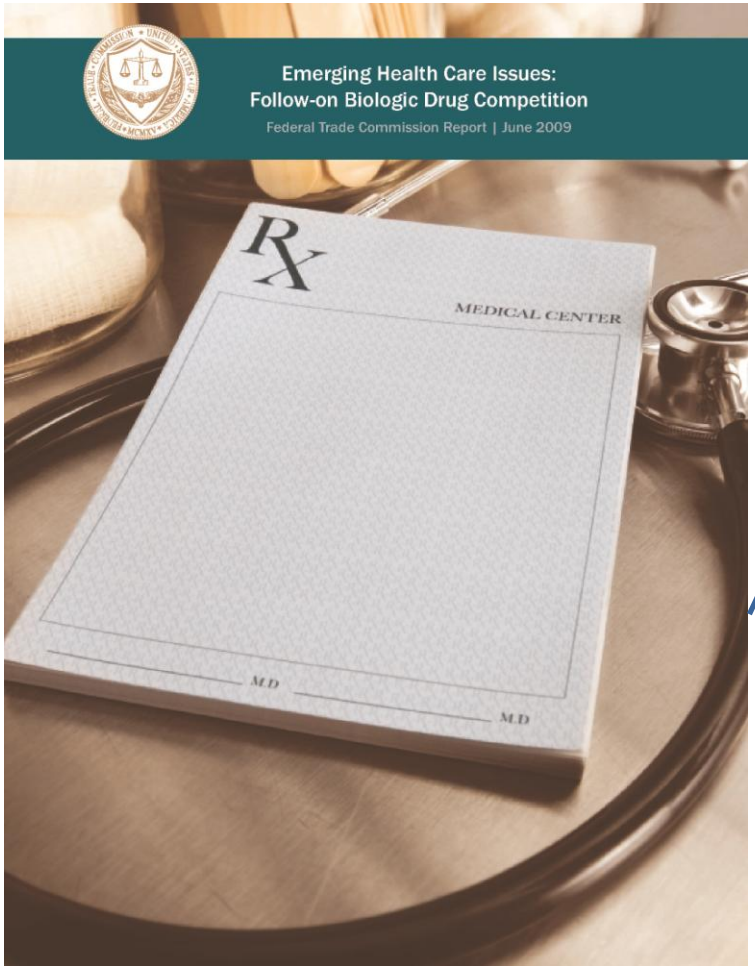
- FTC Expertise
- **Enforcement**
- Competition Advocacy
- Ways the FTC Can Help in the FOB Debate
- FTC Analysis of Patient Safety Claims

# FTC Enforcement – Small Molecule Drugs

- Conduct
  - Patent settlements under Hatch-Waxman Act
- Merger Enforcement
  - Shaped by knowledge gained from FTC policy studies

Example: FTC mail order pharmacy study

# FTC Enforcement – Follow-on Biologics




"A pre-approval patent resolution process in the FOB context could facilitate collusive agreements."

# FTC Enforcement – Follow-on Biologics

DechertOnPoint

April 2010 / Special Alert

A legal update from Dechert's Antitrust/Competition and Intellectual Property Litigation Groups

**Health Care Reform Includes Biologics Price Competition and Innovation Act of 2009**

**Clears Path for Follow-on Biologic Competition, Raises New and Familiar Antitrust Issues**

**Key Points and Possible Action Items**

- The new law creating a pathway for the expedited entry of biosimilar versions of branded biological products will profoundly affect competition between biotechnology firms.
- The law creates antitrust risk by requiring competitors to exchange competitively sensitive information related to possible patent disputes. Antitrust counsel should be consulted in connection with such exchanges.
- Innovators should also consult antitrust counsel over planning and execution of competitive strategies in response to attempted entry by FOB manufacturers.

President Obama signed into law on March 23, 2010 the Patient Protection and Affordable Care Act, which included the Biologics Price Competition and Innovation Act of 2009 ("Biologics Act"). By clearing a regulatory path for expedited entry by "biosimilar" versions of branded biological products (called "follow-on biologics" or "FOB products"), the Biologics Act will profoundly affect competition between biotechnology firms in the development, manufacture and sale of biologic products—those therapeutic drugs that are protein-based and derived from living matter or manufactured in living cells using recombinant DNA biotechnologies.

Key features of the Biologics Act, particularly for purposes of assessing antitrust risks, include: (1) a 12-year exclusivity period for the innovator biological product; (2) one year exclusivity for an "interchangeable biosimilar product"; (3) procedures to determine the extent of patent disputes between the innovator and the FOB manufacturer; and (4) provisions that require information sharing between innovator firms and FOB manufacturers. These features will undoubtedly raise a number of antitrust issues, some of which have become a common feature in the world of small molecule pharmaceuticals. To help mitigate antitrust risks associated with the Biologics Act, counsel familiar with the antitrust laws, the FTC's views on FOB competition, intellectual property rights in biologics, and patent settlements in general should be consulted early in the Biologics Act process.

**Summary of the Biologics Act**

The Biologics Act establishes a pathway for the regulatory approval of biosimilar and interchangeable biological products that is loosely modeled on the Abbreviated New Drug Application (ANDA) process for small molecule drugs, which was enacted through the Hatch-Waxman Act Amendments to the

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- Areas for potential FTC enforcement were outlined in 2010 Dechert OnPoint
- Risk of collusion in the information exchange process
- Citizen petitions to FDA
- Misleading marketing regarding product differences

# Outline

- FTC Expertise
- Enforcement
- **Competition Advocacy**
- Ways the FTC Can Help in the FOB Debate
- FTC Analysis of Patient Safety Claims

# FTC Competition Advocacy

- Statements to U.S. Congress
  - FTC submitted 2009 report to Congress
  - Report was subject of hearings
- Comments to state legislatures
  - Comments on state law proposals to regulate PBMs

# FTC Competition Advocacy (continued)

- Comments to federal agencies
  - FTC comments to FDA regarding Hatch-Waxman enforcement
- Workshops, hearings, & reports
  - 2009 Report (and preceding public workshop)

Report recognized that “Pioneer manufacturers, potential FOB manufacturers, and payors were virtually unanimous in their predictions that competition from FOB drug entry is likely to resemble brand-to-brand competition, rather than brand-to-generic competition”

# Outline

- FTC Expertise
- Enforcement
- Competition Advocacy
- **Ways the FTC Can Help in the FOB Debate**
- FTC Analysis of Patient Safety Claims

# Ways the FTC Can Help in the FOB Debate

- Written comments to FTC due on March 1
- Empirical papers (outside the comment period)
  - Funded by the company or trade association
  - Third party, peer reviewed papers
- In-person meetings with FTC to educate
  - Key developments
  - Company management
- Shape FTC views on ongoing regulatory developments
  - FDA
  - State legislation
  - Congress

Example: Hospital Mergers

# Outline

- FTC Expertise
- Enforcement
- Competition Advocacy
- Ways the FTC Can Help in the FOB Debate
- FTC Analysis of Patient Safety Claims

# FTC Analysis of Patient Safety Claims

- Statements of company leadership
  - Public statements and internal statements
- Trade association statements
- Views of industry experts
- Empirical studies

Examples:
- ❖ Mail Order Pharmacy
- ❖ REMS
- ❖ Teeth Whitening

# Presenters

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