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LDG ATTORNEYS AT LAW

The Hatch-Waxman Act
Statutory Framework and Procedures

Emily Rapalino, Goodwin Procter LLP
Nicholas Mitrokostas, Goodwin Procter LLP
Michael Patunas, Lite DePalma Greenberg LLC

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Agenda

- Introduction to Hatch Waxman
- ANDA Pre-litigation and Litigation Timeline & Procedures
- Effects of Hatch-Waxman Legislation
- Unintended Consequences of Hatch-Waxman that led to 2003 Amendments
- Recent Trends in Hatch-Waxman Law

Introduction

- ANDA Litigation: What is it?
  - Patent litigation between brand name and generic pharmaceutical companies
  - Fight over the market for big-selling pharmaceutical products:

The Hatch-Waxman Act

- **Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) enacted to balance two important public policy goals:**
  - Provide period of patent and marketing exclusivity to brand (innovator) drug manufacturers to enable them to recoup investment in drug development
  - Provide consumers with benefit of rapid availability of lower priced generic versions of innovator drugs
- **Amended in 2003 by the Medicare Modernization Act of 2003 Title XI to remedy some of the abuses resulting from original Hatch-Waxman Act**

Before the Hatch-Waxman Act

- Challenges for brand name pharmaceutical companies:
  - Lengthy FDA approval time for new drugs
  - Shortened “effective” life of patents covering drugs
  - Insufficient exclusivity to recoup R&D investment

- Challenges for generic pharmaceutical companies:
  - FDA approval process long and costly
  - Could not begin development until after brand patent expiration

Why Did Congress Step in To Create Special Procedures For Brand-Generic Litigation?

Importance of pharmaceuticals to public

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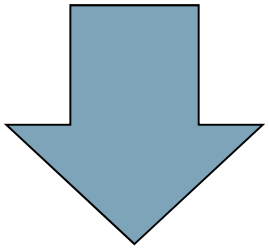
Rigors of drug approval process



Incentives to brand and generic drug companies

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Premarketing litigation

The Parties to ANDA Litigation

- Innovator: Files New Drug Application (NDA)
  - Includes full studies of safety and efficacy conducted by the applicant (or studies that applicant has a right of reference to)

- "Generic" Challenger: Files an Abbreviated New Drug Application (ANDA) to make generic version of innovator product
  - Must demonstrate bioequivalence
  - Can use safety and efficacy studies from the NDA (innovator data)
  - Must have identical active ingredient, route of administration, labeling, use
  - Another route: Paper NDA under 505(b)(2)

Advantages of ANDA products

- Once a generic launches under an ANDA application, pharmacies will replace the innovator drug with the generic substitute
- Substitution can be mandated by state law
- Prescriptions written by doctors for the brand generally will be filled with the generic by the pharmacist
- Generic products under ANDAs do not need marketing

NDA Holder - Patent Listing

- NDA applicants must inform FDA of patents covering the approved product/method
- "Orange Book Listing"- the FDA publishes the patents in the Orange Book ("Approved Drug Products with Therapeutic Equivalence Evaluations")
  - Listed patents must claim the approved product or the drug substance in the approved product
  - Method of use claims must cover the approved method
  - Polymorphs can be listed if bioequivalent to approved form
  - Process/manufacturing patents can **not** be listed

Orange Book:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

Orange Book Listing Mechanics

- Submit patent information on proper forms
  - FDA Forms 3542 or 3542a, see http://www.fda.gov and search for "forms“
- Declaration required
  - Signed verification under penalty of perjury
- Must submit patent information within 30 days after approval of NDA or supplement (21 C.F.R. § 314.53(c))
- For patents that issue after submission, but before approval, of NDA, or after approval of NDA, must submit patent information within 30 days of patent issuance (21 C.F.R. § 314.53(d))

Orange Book Listing

FDA Home[3] Drug Databases[4] Orange Book[5]

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Patent and Exclusivity Search Results from query on Appl No 021880 Product 006 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021880	006	5635517	Oct 4, 2019	Y	Y	U - 1211	
N021880	006	6045501	Aug 28, 2018			U - 1210	
N021880	006	6281230	Jul 24, 2016			U - 1212	
N021880	006	6281230	Jul 24, 2016			U - 1414	
N021880	006	6315720	Oct 23, 2020			U - 1210	
N021880	006	6555554	Jul 24, 2016		Y	U - 1211	
N021880	006	6561976	Aug 28, 2018			U - 1210	
N021880	006	6561977	Oct 23, 2020			U - 1210	
N021880	006	6755784	Oct 23, 2020			U - 1210	
N021880	006	6908432	Aug 28, 2018			U - 1210	
N021880	006	7119106	Jul 24, 2016		Y		
N021880	006	7189740	Apr 11, 2023			U - 1215	
N021880	006	7465800	Apr 27, 2027	Y	Y		
N021880	006	7468363	Oct 7, 2023			U - 1414	
N021880	006	7855217	Nov 24, 2024	Y	Y		
N021880	006	7968569	Oct 7, 2023			U - 1216	
N021880	006	8204763	Aug 28, 2018			U - 1249	
N021880	006	8288415	Jul 24, 2016	Y	Y		
N021880	006	8315886	Oct 23, 2020			U - 1249	
N021880	006	8404717	Apr 11, 2023			U - 1215	
N021880	006	8530498	May 15, 2023			U - 1216	
N021880	006	8589188	Aug 28, 2018			U - 1210	
N021880	006	8626531	Oct 23, 2020			U - 1210	
N021880	006	8648095	May 15, 2023			U - 1216	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021880	006	I - 672	Jun 5, 2016
N021880	006	NS	Jun 5, 2016
N021880	006	ODE	Jun 5, 2020

ANDA – Patent Certifications

- ANDA (generic) applicants must then make one of the following certifications for each Orange Book listed patent:
  I. No patent information listed
  II. Listed patent has expired
  III. Will not market until the listed patent expires
  IV. That the listed patent is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of the drug product for which the abbreviated application is submitted [a "Paragraph IV Certification"]
- Can file Paragraph III certification for some patents and Paragraph IV certification for others
- First ANDA Paragraph IV filer obtains 180 day marketing exclusivity against other ANDA filers

ANDA – Patent Certifications

- Need to consider non-Orange Book listed patents as well!
  - NDA holder can bring declaratory judgment action for infringement of non-Orange Book listed patents (e.g., process patents)

- Need to monitor NDA holder's pending patent applications
  - If "new" product; and/or
  - new process for making the product and/or
  - new test for purity, etc., is developed – that may be patentable

- "Pop-up" Orange Book patents

ANDA Notice Letter/Detailed Statement

- "All Paragraph IV ANDA filers must provide notice of their Paragraph IV certification to both the patent owner and the NDA holder. This notice must set forth a 'detailed statement of the factual and legal basis for the opinion of the applicant that the patent is invalid or will not be infringed.'"
  - *Caraco Pharm. Labs. Ltd. v. Forest Labs., Inc.*, 2008 WL 850330 *2 (Fed. Cir. 2008)(citing 21 U.S.C. § 355(j)(2)(B))
- ANDA filer must send its Notice Letter to NDA holder/patent holder within 20 days of receiving ANDA No. from FDA
- Offer of Confidential Access (OCA) accompanying Notice Letter
  - Provides jurisdiction for Declaratory Judgment action

Hatch Waxman: Pre-Litigation Timeline

- Filing ANDA with a paragraph IV certification is “artificial” act of patent infringement
- NDA holder/patent owner has 45 days from receipt of Paragraph IV notice to sue for infringement
- If suit is brought within the 45 days, 30-month stay of FDA approval of the generic application (suit may be brought after 45 days with no stay)
- Termination of stay before 30 months if:
  - District court holds patent is invalid, not infringed, or no claim for patent infringement exists
  - Appellate court holds patent is invalid, not infringed, or no claim for patent infringement exists
  - Date of entry of settlement or consent decree stating the patent is invalid or not infringed

Hatch Waxman: 180 Day Exclusivity

- Hatch Waxman gives first ANDA applicant with Paragraph IV certification 180 days of exclusivity from competition by other generic ANDA applicants

- No other generic application can be approved by FDA until 180 days after first filer achieves favorable court ruling or launches its product

- 180 day exclusivity is highly lucrative for first filer

Hatch Waxman – section viii carveout

"Section viii" Statements - 21 U.S.C. § 355(j)(2)(A)(viii)

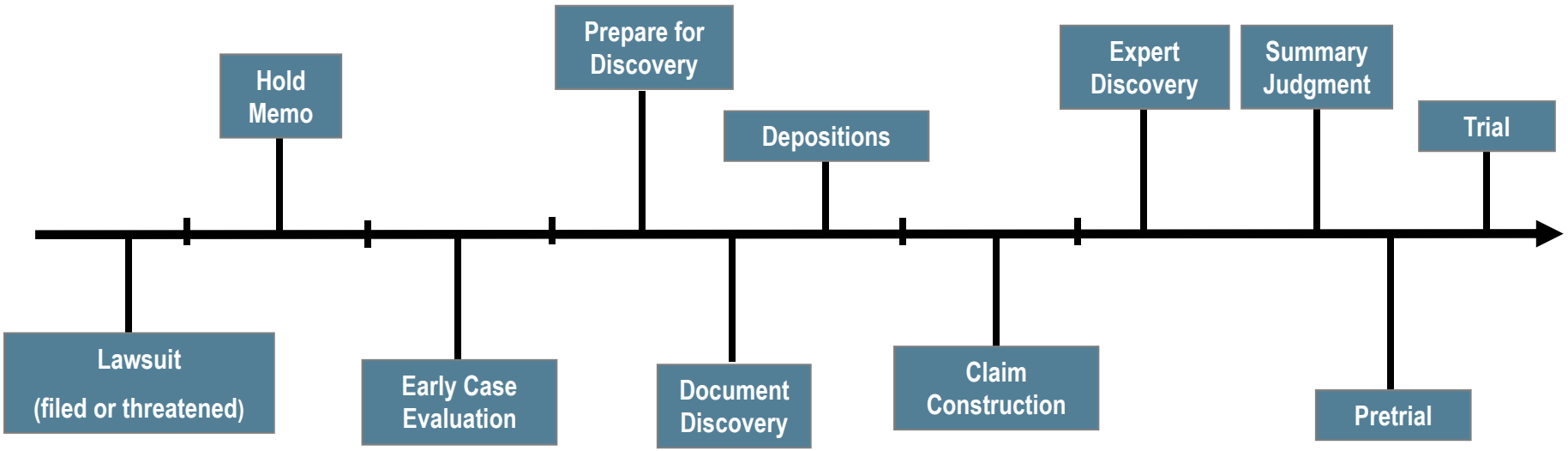
- A statement that the generic applicant seeks to market the drug for a use other than the patented use
- An alternative to the Paragraph I through IV certification required when seeking to market drug for a patented use

- Under this procedure:
  - No duty to provide notice to innovator
  - No 30-month stay of FDA approval
  - No 180-day exclusivity period to successful first applicant

ANDA Litigation Process

- The Life of an ANDA Case
  - ANDA with Paragraph IV certification
  - Notice Letter within 20 days of ANDA acceptance
  - Complaint filed within 45 days of Notice Letter receipt
  - Fact discovery
    - Document discovery, electronic discovery
    - Depositions
  - Expert discovery
  - Summary Judgment
  - Trial
  - Settlement (?)

ANDA Litigation: Patent Litigation Timeline



ANDA Litigation

- No right to jury trial because there are no damages
- No willful infringement based on ANDA filing
  - *Glaxo Group Ltd. v. Apotex, Inc.*, 375 F.3d 1339, 1351 (Fed. Cir. 2004)
- All defenses available as in any patent litigation (anticipation, obviousness, § 112 defenses, inequitable conduct, non-infringement)
- Defenses NOT limited to those in Detailed Statement
  - *Smithkline Beecham Corp. v. Apotex Corp.*, 2000 WL 116082 *8 (N.D. Ill. Jan. 24, 2000).
- Full discovery (including e-discovery)

ANDA Litigation - Resolution

- At-risk launch possible after end of 30 month stay
  - *Abbott Labs., Inc. v. Sandoz, Inc.*, 529 F. Supp. 2d 893, 899 (N.D. Ill. 2007) (plaintiff sought damages after launch by generic)
- Preliminary Injunctions have been granted in some ANDA cases to prevent at-risk launch
  - *See, e.g., Ortho-McNeil Pharm., Inc. v Mylan Labs., Inc.*, 2006 WL 3019689 (DNJ 2006)
- 30 month stay terminated upon decision of District Court in defendant's favor.
  - 21 U.S.C. § 355(j)(5)(B)(iii)

Goals of Hatch-Waxman Legislation

- The Hatch-Waxman Act was enacted in 1984
- Goals:
  - Spur new pharmaceutical development
  - Encourage greater public access to generic drugs

Provisions Favorable to Branded Drug Manufacturers

- Patent term restoration for time drug spent in approval and 50% testing time
  - A patent term can be extended only once, up to max of 5 years (can't be extended beyond 14 years)
  - Only one patent can be extended for a given regulatory review period
  - Product by process only if product is a NCE
  - Method of treatment (limited to FDA approved indication for drug)
- Non-Patent-Based Exclusivities
  - E.g. NCE, NP, Orphan drug, and Pediatric exclusivity
- Notice Requirements
  - Orange Book Listings
  - Patent Certifications by ANDA-Applicants
- Automatic Injunctions
  - 30-month stay

Provisions Favorable to Generic Drug Manufacturers

- Abbreviated New Drug Applications – ANDA
  - Only need to demonstrate therapeutic equivalence
- 180-Day Period of Exclusivity
  - First ANDA-applicant to make a paragraph IV certification
- Safe Harbor for Regulatory Review Testing
- Declaratory Judgment Action
  - DJ can be brought after 45-day notice period for patent owner has expired
- Counterclaim for Delisting
  - Seek to order patent holder to correct or delete Orange Book listing

Effects of Hatch-Waxman Legislation

- Nearly all top-selling non-patented, branded drugs face generic competition
  - Pre-Hatch-Waxman, only 35% faced generic competition
- The vast majority of prescriptions today are for generics
  - Pre-Hatch-Waxman, only 15% of prescriptions were for generics
- Generic prices are approximately 60% less than branded prices
- Rapid generic substitution, 80% conversion within 6-8 weeks*
- Generic companies have significantly increased research and development of generic drugs, increase in patent applications by generic companies

*Silver R, A Wall Street Perspective on Generics, 2007 GPhA Meeting, March 1-3, 2007, available at www.gphaonline.org/AM/CM/ContentDisplay.cfm?ContentFileID=593

Effects of Hatch-Waxman Legislation

- Multiple generic companies can file an ANDA on the same day and share the 180-day exclusivity period
- "Authorized Generics" share profits from 180-day exclusivity period with branded drug manufacturer
  - Lessens incentives for other generic companies to file ANDAs
- Antitrust issues arise with "Reverse Payment" agreements in which branded companies pay generic companies to not file an ANDA or to stay out of the market
- Branded companies registering multiple patents that cover the same drug to keep generic companies at bay
  - "Life cycle management"

Unintended Consequences of Original Hatch-Waxman Statute

- Multiple 30-Month Stays
- Improper Orange Book Listings
- Parking of 180-Day Co-Exclusivity
- Suspect Settlement Agreements Between Brands and Generics
    - LED TO…
- 2002 FTC Generic Drug Study
- June 2003 Amendment of FDA Regulations Governing Patent Submission and Listing Requirements and Application of 30-Month Stays (*68 Fed. Reg. 36676-712; 21 C.F.R. § 314)*
- **Major Overhaul of ANDA Statute in Title XI of the Medicare Prescription Drug Improvement and Modernization Act of 2003**

Medicare Prescription Drug Improvement and Modernization Act of 2003

- Limits innovator to one 30-month stay per ANDA
  - Pop up patents do not extend innovator exclusivity
  - Can still bring suit on pop up patents
- Restructures the 180-day exclusivity provisions for first-filed ANDAs
  - Forfeiture of Exclusivity
  - Multiple “First Applicants”
  - New Triggering Events
- Allows generic to file declaratory judgment action if innovator fails to bring suit within 45 days
- Requires filing of agreements between innovators and generics with FTC

Recent Trends in ANDA litigation

- Expanding scope of the safe harbor
- Limiting scope of electronic discovery
- Tailored local patent rules in some jurisdictions
- Parallel ITC Actions
- Parallel PTAB proceedings (Inter Partes Review), especially by non first-filers

Product Development: Safe Harbor Exception

- Safe Harbor Provision: 35 U.S.C. § 271(e)
  - It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses ***reasonably related to the development and submission of information under a Federal law*** which regulates the manufacture, use, or sale of drugs or veterinary biological products.
- Recent case law has expanded the scope of what is included within the safe harbor protection.
  - Early stage preclinical research. *Merck v. Integra (SCt 2005)*
  - Post-approval testing where information is generated for FDA. *Momenta v. Amphastar (Fed.Cir. 2012)*

Limiting Scope of Electronic Discovery

- The Problem: Exponential increase in volume and burden of discovery with advent of "e-discovery." Costly and inefficient.
- Federal Circuit Advisory Council adopted a Model Order Regarding E-Discovery in Patent Cases in September 2011, including guidelines for district courts.
- Since then, some district courts have adopted their own model rules:
  - Eastern District of Texas, Model Order Regarding E-Discovery in Patent Cases, February 27, 2012. Since then more than 100 cases have applied it
  - N.D. California, no local model rule, but some cases have applied Federal Circuit Model Order
  - Some districts limit scope of e-discovery by limiting sources of ESI to be collected, number of custodians, number of search terms
- BUT NOTE: Electronic sources of information still need to be preserved and caution should be exercised in what is documented electronically and in preservation efforts

Local Patent Rules

- 30 U.S. district courts have adopted local rules specific to patent cases
- 6 of these jurisdictions have tailored specific local patent rules that apply to Hatch-Waxman cases
- In general, local patent rules require parties to articulate positions (claim construction and contentions) early in the case.
- Many of the Hatch-Waxman specific rules require generic defendants to serve their contentions first

Parallel ITC Actions

- Currently not a popular forum for pharmaceutical litigation
  - Benefit to the innovator (who chooses the forum) of district court litigation under Hatch-Waxman is the 30 month stay – slows generic entry.
  - ITC actions are generally quick with decision within 14 months
- ITC actions more likely for non-Orange Book process patents infringed overseas. The trade statute governs this, 19 U.S.C. §1337(a)(1)(B)(ii), and is adjudicated by the ITC
- Defenses available in district court under 35 U.S.C. §271(g) are not available in the ITC. *Kinik Co. v. Int'l Trade Commission*, 362 F.3d 1359 (Fed. Cir. 2004).
- However, analogous defenses may very well be available in the ITC under the trade statute. *Certain Sucralose, Sweeteners Containing Sucralose, and Related Intermediate Compounds Thereof*, Inv. No. 337-TA-604, Comm'n Op. (Apr. 29, 2009).

Parallel PTAB Proceedings

- Approx. 2% of total IPR petitions filed to date were filed on patent involved in Hatch-Waxman litigation. Number is growing.
- Lower cost, faster pathway to decision on invalidity
- Lower burden or proof at the PTAB (preponderance of the evidence)
- Most often challenged patents – formulation/composition patents (then method of use, then compound patents)
- Most often used by non-first filers
- Some IPRs result in stay of parallel district court cases; implication for statutory 30 month stay

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Orange Book Issues: Listing, De-Listing, And Carve-Outs

Emily Rapalino, Goodwin Procter LLP
Nicholas Mitrokostas, Goodwin Procter LLP
Michael Patunas, Lite DePalma Greenberg LLC
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What is the Orange Book?

- FDA publication formally titled ***Approved Drug Products with Therapeutic Equivalence Evaluations***
  - Lists patents covering approved drugs
  - Originally published annually with orange cover
  - Now searchable online, updated regularly

- Nearly all approved OTC and prescription drugs have Orange Book listings*

*Exceptions: pre-FDA Act (1938) drugs and drugs approved for safety only from 1938-62 (DESI drugs)

What is Inside the Orange Book?

- For listed drugs, the Orange Book includes:
  - Trade name and active ingredient(s)
  - NDA (approved application number) and NDA owner
  - **Patents claimed** to cover drug and their expiration date
  - **Patent use code** (usually label indication of use)

- For listed generic products, the Orange Book also includes therapeutic equivalence codes
  - "AB" codes mean drug can be substituted in most states
  - "B" codes mean that bioequivalence *not* demonstrated

Who Decides What Patents Are Listed?

- NDA owners list their own Orange Book patents:

  "The applicant shall file with the [NDA] application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted…"

  – 35 U.S.C. § 355(b)(1)

- Later-issued patents are added by NDA owners as they are obtained. *See Allegran, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1325-26 (Fed. Cir. 2003)

What Patents Can Be Listed In the Orange Book?

FDA has promulgated regulations regarding Orange Book listing.

21 C.F.R. § 314

Listable Patents

- Active ingredient
- Formulation
- Composition
- Method of approved use
- Method of treatment

Nonlistable Patents

- Processes
- Packaging
- Metabolites
- Intermediates
- Medical devices

What Patents Can Be Listed In the Orange Book?

Patents That* Sometimes *Can Be Listed In Orange Book

- Product-by-Process Patents
  - A product-by-process patent claims a product by describing or listing process steps to wholly or partially define the claimed product.
  - A product-by-process patent **must claim a "novel" product to be listed in the FDA's Orange Book.** *See* Food & Drug Administration Final Rule for 21 C.F.R. § 314.
- Polymorph Patents – "For patents that claim a polymorph that is the same as the active ingredient described in the approved or pending application, the applicant shall certify . . . that the applicant has test data . . . demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the new drug application." *See* 21 C.F.R. § 314.53 (b)(1)

What Patents Can Be Listed In the Orange Book?

- Listed patents must claim the *approved* product or active ingredient
- Method of use claims must cover an approved method
- Process/manufacturing patents can *not* be listed

That said, FDA does not evaluate Orange Book patent listings or patent use codes!

- FDA simply publishes patents information provided by NDA holder

FDA's Role is Purely Ministerial: *Alphapharm Pty Ltd. v. Thompson*

- Alphapharm submitted an ANDA for generic citalopram with a paragraph IV certification against Forest's '884 patent. The FDA refused to review the ANDA because the '884 patent was not listed in the Orange Book.

  2004 WL 1810956, at *4 (D.D.C. Aug. 13, 2004)

- Forest refused to have the '884 or other patents listed because they did not claim the drug, drug product, or method of use.
- Court found FDA's acceptance of nothing more than a "ministerial role" in patent listing to be a reasonable interpretation of the statute

Listing Patents for Drug Delivery Devices

- Does a listable "approved drug product" patent include one for devices to deliver a drug?
- FDA Rules specifically allow listing of certain drug delivery device patents such as ''metered aerosols, capsules, metered sprays, gels and pre-filled drug delivery systems.'' Patent Submission Rules for Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. at 36,680.
  - Based the definition of ''drug product'' found in FDA regulations, ''drug product'' is ''a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.'' 21 CFR § 314.3 (2011),
  - The ''key factor'' in determining whether a patent must be listed is ''whether the patent being submitted claims the finished dosage form of the approved drug product.'' *Id.*
  - Look at whether the device/packaging is an "integral part" of the approved product
- Despite Citizen's Petitions requesting clarification on the scope of device/packaging patents that are Orange Book listable, FDA has not provided additional guidance.

Options Available to ANDA Filers For Patents Listed in Orange Book

1. Wait for patent expiration (Paragraphs, I, II, III)
2. Challenge patents (Paragraph IV)
3. Carve-out patent use (Section viii Statement)
4. Counterclaim to delist/correct Orange Book patent information

Options for Addressing Patents Listed in Orange Book
1. No Challenge to Orange Book Patents

- Certifications that do not trigger potential litigation:
  - Paragraph I: no OB patents listed
  - Paragraph II: listed OB patent has expired
  - Paragraph III: approval sought *after* expiration of listed patent

Not to challenge

> "An ANDA containing a Paragraph III certification indicates that the applicant does not intend to market the drug until after the expiration of the patent, and the approval of the ANDA cannot be made final until the patent expires." *Mylan Pharm. v. Thompson*, 268 F.3d 1323, 1327 (Fed. Cir. 2001); *see* 21 U.S.C.A. § 355(j)(2)(A)(viii)(III).

Options for Addressing Patents Listed in Orange Book
2. Paragraph IV

Challenge Patent Under Paragraph IV

- **Paragraph IV** – "All Paragraph IV ANDA filers must provide notice of their Paragraph IV certification to both the patent owner and the NDA holder. This notice must set forth a 'detailed statement of the factual and legal basis for the opinion of the applicant that the patent is invalid or will not be infringed.'" *Caraco Pharm. Labs. Ltd. v. Forest Labs., Inc.*, 2008 WL 850330 *2 (Fed. Cir. 2008) (citing 21 U.S.C. § 355(j)(2)(B)).
- *See also* 21 C.F.R. § 314.95 ("For each patent . . . the applicant certifies under 314.94(a)(12) is invalid, unenforceable, or will not be infringed, the applicant shall send notice of such certification by registered or certified mail [to the NDA holder and patent owner]. . . .").

- No Orange Book listing = no PIV certification required
  - No jurisdiction for suit under § 271(e)(2)(A)
  - No 30 month stay of approval

Options for Addressing Patents Listed in Orange Book
3. Section viii Carve-Out

- What if the FDA has approved a use that is not patented, but there are other patents listed in Orange Book?
  - For example, a drug approved as antidepressant may list patents for treatment of social anxiety disorder
  - Does an ANDA applicant need to provide Paragraph IV certification for the patents covering uses that do not provide basis for approval?
    Not necessarily…

- ANDA filer can "carve out" the other patents from the proposed label and win approval from FDA *without* certifying under Paragraphs I-IV.

Options for Addressing Patents Listed in Orange Book
3. Section viii Carve-Out

Section viii Statements

- As an alternative to a Paragraph I-IV certification, an ANDA applicant may certify to FDA that it does not seek approval for a method of use claimed in Orange Book listed patents for the drug. 21 U.S.C.A. § 355(j)(2)(A)(viii) ("Section viii Statement")
- The applicant must omit or "carve out" from its label information pertaining to the protected use. *See* 21 CFR 314.92(a)(1) and 314.94(a)(12)(iii).
- Such a carve out does not violate the "same labeling" requirement for an ANDA as long as it does not "render the application less safe or effective for the remaining non-protected conditions of use"
  - FDA makes this determination
  - Input from brand not sought by FDA, but brand often files citizen's petition

Options for Addressing Patents Listed in Orange Book
3. Section viii Carve-Out

Purepac Pharm. Co. v. Thompson, 354 F.3d 877, 880 (D.C. Cir. 2004)

> "A section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent."

AstraZeneca v. Apotex, 669 F.3d 1370 (Fed. Cir. 2012)

- Apotex certified that it only sought FDA approval for non-patented methods of using AZ's cholesterol-lowering drug Crestror (rosuvastatin)
- Apotex argued that its ANDA did not constitute infringement because of the proposed carve-out District court agreed with Apotex and dismissed
- The Federal Circuit, 2-1 (Judge Newman dissenting) found arguments were not ripe, and affirmed dismissal on basis that an **ANDA seeking to market a drug for unpatented methods cannot infringe a method patent under § 271(e)(2)(A)**

Options for Addressing Patents Listed in Orange Book
3a. Advantages of Section viii Carve-Out

- Carve out allows a generic company to eliminate indications from its label even though the brand has all of the specified indications
- Once approved, drug can be prescribed for any reason

  > FDA has "long-standing policy of not interfering with the practice of medicine, in particular with physicians' ability to prescribe approved drug products for their patients for any purpose deemed appropriate…" – *Denial of Citizen Petition, July 28, 2008 letter from Janet Woodcock, CDER, Docket No. 2008P-0069*

- If FDA allows *all* patented uses to be carved out:
  - No Paragraph IV certification is required from ANDA filer
  - Therefore, jurisdiction under 35 U.S.C. § 271(e)(2)(A) not triggered
  - Thus, NDA holder cannot sue to receive automatic 30-month stay

Options for Addressing Patents Listed in Orange Book
3b. Disadvantages of Section viii Carve-Out

- FDA may not allow carve-out at all
  - FDA may only approve a generic label carving out a patented method of use if it determines that differences to the listed drug label "do not render the proposed drug less safe or effective than the listed drug for all remaining non-protected conditions of use." 21 CFR 314.127(a)(7).
  - During pendency of application, FDA may issue deficiency letter requiring changes or additions to label
    - FDA does not consider whether changes might infringe
    - FDA only considers safety/efficacy

Options for Addressing Patents Listed in Orange Book
3b. Disadvantages of Section viii Carve-Out

- Launch based on carve out is “at-risk”
  - Patent owner may sue under ordinary inducement and contributory infringement theories
  - May seek TRO and preliminary injunction against launch
  - Brands may use non-OB listed patents in this manner
- Even if carve out is allowed, **FDA may require labelling that supports restraining order and preliminary injunction for induced infringement claims**

Options for Addressing Patents Listed in Orange Book
3b. Disadvantages of Section viii Carve-Out

Cautionary example: *AstraZeneca v. Apotex* (Fed. Cir. 2010)

- AZ pat. covers once-daily administration of asthma drug budesonide
- Prior art use was twice-daily administration
- Apotex submitted section viii statement specifically asserting that it was not seeking approval for the once-daily method of use claimed in the AstraZeneca patents
  - Proposed label contained no explicit mention of once-daily use
  - However, the labelling language regarding downward titration—using lowest effective dose—was be retained, as required by the FDA
- AZ filed a declaratory judgment (non-271(e)(2)(A)) action and sought preliminary injunction against sale of generic budesonide
  - Key issue: whether label could show "specific intent" for inducement

Options for Addressing Patents Listed in Orange Book
3b. Disadvantages of Section viii Carve-Out

***AstraZeneca v. Apotex,* 633 F.3d 1042 (Fed. Cir. 2010) - cont.**

- Specific intent for inducement
  - "[W]here a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when [alleged inducer] has actual knowledge that some users of its product may be infringing…" *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).
  - However, "liability for active inducement may be found 'where evidence goes beyond a product's characteristics or the knowledge that it may be put to infringing uses, and shows statements or actions directed to promoting infringement." *Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1341 (Fed. Cir. 2008)
- District court found AZ likely to succeed on merits, and granted PI
  - Apotex presented testimony about its efforts to win FDA approval for a non-infringing label, but district court reaffirmed its decision

Options for Addressing Patents Listed in Orange Book
3b. Disadvantages of Section viii Carve-Out

***AstraZeneca v. Apotex,* 633 F.3d 1042 (Fed. Cir. 2010) - cont.**

- Federal Circuit affirmed preliminary injunction
  - Pertinent question is whether the proposed label instructs users to perform the patented method
    - If so, the proposed label may provide evidence of affirmative intent to induce infringement
    - Here, court found that downward titration language would inevitably lead some to reduce administration to once daily of smallest dose
  - Fact that FDA required language is not excuse an excuse
    - Apotex had other options: (1) Submit a PIII certification, (2) PIV certification, (3) formally appeal adverse FDA decision on titration language, or (4) file a 355(b)(2) "paper NDA" seeking approval for lesser doses to avoid titration to once-daily dosing
    - Could also abandon effort to launch drug

Options for Addressing Patents Listed in Orange Book
4. Counterclaim to Correct Orange Book Listing

- What prevents companies from listing irrelevant patents in the Orange Book to hinder generic competition?
- Counterclaim provision to Hatch-Waxman Act

  > "the applicant may assert a counterclaim seeking an order requiring the [brand company] to correct or delete the patent information [it] submitted . . . [to the FDA] on the ground that the patent does not claim . . . an approved method of using the drug." – 21 U.S.C. § 355(j)(5)(C)(ii)(I).

- This provision was added in 2003, but meaning was uncertain until 2012 *Caraco* decision by Supreme Court

Counterclaim Provision of Hatch-Waxman Act
4. Caraco v. Novo Nordisk

Facts

- NDA owner Novo had two patents listed in Orange Book for Prandin (repaglinide)
  - Patent for repaglinide itself, expiring in 2009
  - Patent for repaglinide in combination with metformin, exp. 2018

- Caraco filed ANDA with PIII for repaglinde patent and proposed carve-out for the metformin combination indication
  - In response, Novo revised Orange Book-listed patent use code
    - Combination patent previously (and accurately) listed for use of combination therapy of repaglinide and metformin
    - New code for combination patent was much broader: "a method for improving glycemic control in adults with Type 2 diabetes"
    - FDA duly entered change into the Orange Book
  - With revised code, FDA refused Caraco's proposed carve-out

Counterclaim Provision of Hatch-Waxman Act

4. Caraco v. Novo Nordisk

What is a patent use code?

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020702	001	4681893	Sep 24, 2009	Y	Y	U - 161	
N020702	001	4681893*PED	Mar 24, 2010			U - 161	
N020702	001	5273995	Dec 28, 2010	Y	Y	U - 162	
N020702	001	5273995*PED	Jun 28, 2011			U - 162	
N020702	001	5686104	Nov 11, 2014		Y	U - 213	
N020702	001	5686104*PED	May 11, 2015			U - 213	
N020702	001	5969156	Jul 8, 2016	Y			
N020702	001	5969156*PED	Jan 8, 2017				
N020702	001	6126971	Jan 19, 2013				
N020702	001	6126971*PED	Jul 19, 2013				
N020702	001	RE40667	Dec 28, 2010	Y			
N020702	001	RE40667*PED	Jun 28, 2011				

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent Use Codes

This page defines the patent use codes.

Code	Definition
U - 161	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT

Counterclaim Provision of Hatch-Waxman Act
4. Caraco v. Novo Nordisk

Litigation History

- After FDA rejected carve-out, Caraco served PIV certification for the combination patent, and was sued by Novo
  - Caraco counterclaimed to have Novo "correct" the Orange Book patent use code so that the combination patent listed only for combination use
  - The district court granted Caraco's counterclaim
    - The district court rejected Novo's assertion that the counterclaim provisions "are limited to a correction of the patent number and the expiration date of the patent"—belied by legislative history
- Federal Circuit reversed in 2-1 split decision
  - Rehearing *en banc* denied, with Judges Gajarsa and Dyk dissenting: "With the majority's blessing, pioneering drug manufacturers now have every incentive to follow Novo's lead and draft exceedingly broad use codes thereby insulating themselves from generic competition and rendering Section viii a dead letter."

Counterclaim Provision of Hatch-Waxman Act
4. Caraco v. Novo Nordisk

- Question Presented to Supreme Court:

  Whether the counterclaim provision of the Hatch-Waxman Act applies when (1) there is "an approved method of using the drug" that "the patent does not claim," and (2) the brand submits "patent information" to the FDA that misstates the patent's scope, requiring "correct[ion]."

- Supreme Court unanimously reversed Federal Circuit
  - Held that the counterclaim provision authorizes a generic manufacturer to "force correction of a use code that inaccurately describes" the NDA holder's patent "as covering a particular method of using the drug in question."

    Caraco Pharm. Labs v. Novo Nordisk, 132 S. Ct. 1670, 1676 (2012)

Options for Addressing Patents Listed in Orange Book
4a. Disadvantages of Orange Book Counterclaim

- Awkward to set up counterclaim suit
  - "If the use code overlaps with the generic manufacturer's proposed carve-out label, FDA will not approve an ANDA with a section viii statement…the generic manufacturer can respond by taking the following steps: submit an ANDA with a paragraph IV certification…wait for the brand manufacturer to institute suit, file a counterclaim, litigate the counterclaim, and if successful in securing the correction of the use code, return to the start of the process and do what it always wanted to do—file an ANDA with a section viii statement and a carve-out label."

    – *Caraco* , 132 S.Ct. 1670, 1688 (Sotomayor, J., concurring)

- Cannot delist product-by-process patents?
  - *See Cadence Parms, Inc. v. Fresenius Kabi USA, LLC*, No. 13-139, Dkt. No. 251 (S.D. Cal. June 5, 2014) (rejecting summary judgment for delisting product-by-process patent of allegedly non-novel product because "attack on the novelty of the product…is also an attack on the claim's validity," so ANDA filer must prove invalidity to delist)

Patent Linkage In Other Jurisdictions

- South Korea's "Green List"
- European Union
- Canada's "Patent Register"
- Singapore
- Other

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Questions?