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Regulatory Exclusivities & Strategies

Major Hatch-Waxman Developments Since Implementation

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Part I: Regulatory Exclusivities

Barriers to Entry

Non-Patent Regulatory Exclusivities

- What are regulatory exclusivities?
  - Period of market exclusivity that is intended to reward the investment of pharmaceutical companies to develop new drugs and/or discover new indications for existing drugs
  - Incentive for companies to to devote the time, money, and resources into new products/indications
  - Allow company to “recoup” time lost to obtaining FDA approval for new product/indication
  - Encourage generic drug makers to develop generic products and reward them for doing so quickly

Barriers to Entry

Non-Patent Regulatory Exclusivities

- Regulatory "exclusivities" that may extend market protection:

Regulatory Exclusivity	Exclusivity Period
First ANDA patent challenger a/k/a "First to File" (FTF)	180 days
New Chemical Entities (NCE)	5 years
New Clinical Investigations (NCI)	3 years
Orphan Drug (ODE)	7 years
Pediatric (PED)	6 months

Hatch-Waxman Framework

The Law

- Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act") provides
  - Partial patent term restoration to compensate innovators for regulatory delays
  - Process to approve generic versions of approved drugs that rely on safety and efficacy data collected by the innovator
  - Framework for disclosure of patent information and patent certifications
  - Regulatory exclusivities for new chemical entities, new clinical investigations and first ANDA patent challenger

Hatch-Waxman Framework

Types of Applications

New Drug Application ("NDA")	Abbreviated New Drug Application ("ANDA")	505(b)(2) NDA Application ("Paper NDA")
Innovator	Generic	Hybrid
Must provide well-controlled clinical studies to demonstrate efficacy	ANDA "piggy-backs" on NDA safety and efficacy studies	Relies upon at least one clinical study conducted by innovator
Preclinical and clinical data showing safety	Must have identical active ingredient, route of administration, dosage form, strength, labeling and intended use	NDA for a modification to an approved drug (e.g., different active ingredient, dosage form, strength, etc.)
Detailed description of manufacturing, packaging and labeling that references clinical studies	Must demonstrate bioequivalence to NDA product	Must contain sufficient data to support the safety/efficacy of the modification
Marketing exclusivities include: NCE, NCI, ODE, PED	Marketing exclusivity only for first-filer and only for 180 days	Marketing exclusivities include: NCE, NCI, ODE, PED

Hatch-Waxman Framework

Triggering the 30-Month Stay

- If generic applicant (ANDA) or 505(b)(2) applicant plans to launch product prior to Orange Book patent expiration, it must certify that the patent(s) are invalid, unenforceable and/or not infringed ("**Paragraph IV**" certification)

- Paragraph IV filer must notify the NDA holder of its certification and provide a **detailed statement** ("DS") explaining the basis for its certification

- The act of filing an ANDA with Paragraph IV certification is considered an act of infringement

Hatch-Waxman Framework

Triggering the 30-Month Stay

- NDA holder (patent owner) has **45 days** to filed lawsuit after receiving the detailed statement
- If lawsuit if brought inside 45 days, **30-month stay** of FDA approval of generic application is triggered
  - 30-month stay may be shortened if a court decision of invalidity, unenforceability or non-infringement occurs before 30-month stay expires
- **One 30-month stay per generic application**, limited to patents listed **prior to the generic application** filing date
  - Generic applicant still has to send notice on patents listed in the Orange Book after the generic application was filed but, if patent holder sues, no extra 30 month stay

Hatch-Waxman Framework

First to File

- First **ANDA** Para IV filer (not 505(b)(2)) obtains **180-day market exclusivity** against other **ANDA** filers (not 505(b)(2)s)
  - Exclusivity triggered by earlier of first commercial marketing of generic drug or brand drug by any "first applicant"
- In order to obtain "First to File" Status:
  - ANDA must be "substantially" complete at time of filing
  - ANDA applicant must "lawfully" maintain a Paragraph IV certification for the drug
- Multiple ANDA applicants may hold exclusivity concurrently on the same drug if they each apply on the same day and file Paragraph IV certifications concerning at least one of the Orange Book listed patents for that drug.
  - This most commonly occurs when multiple applicants file ANDAs on the four-year anniversary of FDA approval of an NDA subject to NCE exclusivity

Hatch-Waxman Framework

First to File

- **Exclusivity Period**
  - First-filer exclusivity blocks final approval of other ANDAs with Paragraph IV certifications for 180 days
  - However, first-filer exclusivity does not apply against an applicant who has filed a Section viii Statement because it is not a Paragraph IV certification.
- **Exclusivity Forfeiture**
  - Failure to market
  - Withdrawal of ANDA (either voluntarily or by FDA)
  - Amendment/withdrawal of qualifying Para IV as to all patents
  - Failure to obtain tentative approval within 30 months
  - Agreement with another ANDA applicant, NDA holder or patent owner adjudicated to violate antitrust laws
  - Expiration of all the patents that are subject of qualifying Para IV of first applicant

New Chemical Entity ("NCE") Exclusivity

- Granted if the FDA has not previously approved the "active ingredient" or "active drug moiety" in any other NDA
  - The active drug moiety is the molecule's active portion and not its variations such as salts or esters
- NCE exclusivity bars FDA from approving an ANDA for **five years** from the first approval of the relevant NDA
  - However, a generic drug company may file an ANDA with a Paragraph IV certification **four years** after the first NDA approval, so long as there is at least one patent listed in the Orange Book

New Clinical Investigations Exclusivity

- Granted when new clinical studies lead to new or changed formulations, dosing regimens or patient population.
- Applicant is entitled to this exclusivity if an application or supplement contains reports of new clinical investigations conducted or sponsored by the applicant that were essential to the approval
  - "Clinical investigations" – human clinical trial
  - "New" – Investigation that has not already been relied upon by FDA to approve another product
  - "Essential to approval" – no other data available that could support approval
  - "Conducted or sponsored by the applicant" – applicant was named sponsor of study or provided 50% or more of the cost of conducting the study
    - Purchase of non-exclusive rights in a study is insufficient

New Clinical Investigations ("NCI") Exclusivity

- This data exclusivity prohibits the FDA from approving a generic drug application for the new dosage form or use for **three years** after the first NDA approval.
  - However, it does not otherwise bar approval of generic drug applications
  - FDA allows generic applicants to exclude from its label an indication that is subject to exclusivity (Section viii)
- Branded drugs may replace old labeling with new labeling only containing new indication to prevent Section viii carve-out

Orphan Drug Exclusivity

How to Get It

- Orphan drug exclusivity was put in place to encourage drug companies to research products for “rare” diseases
- A product is eligible for orphan drug designation if:
  - Treats a disease or condition that affects less than 200,000 people in the US; or
  - There is no “reasonable” expectation that developments costs for the drug product will be recouped from U.S. sales
- This exclusivity period is **seven years**, but only applies to use in treating the specific rare disease or condition
  - Prevents approval of another NDA, ANDA, 505(b)(2) for the same drug for **same disease or condition**

Orphan Drug Exclusivity

How to Get Around It

- 21 C.F.R. § 316.20(a) states:
  - "a sponsor of a drug that is otherwise the same drug as an already approved ***orphan drug*** may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be ***clinically superior*** to the first drug"
- A "**clinically superior**" drug is a drug shown to have greater efficacy, greater safety, or that provides a major contribution to patient care vis-à-vis the previously approved drug, and, by virtue of its clinical superiority, is not considered the "same drug" as the previously approved orphan drug.

Pediatric Exclusivity

- This exclusivity is available if the FDA requests that the NDA holder conduct studies with the drug in pediatric populations.
- Pediatric exclusivity adds **six months** of exclusivity to any marketing or patent exclusivity
  - Runs from expiration (including any extensions) of each Orange Book listed patent
  - Bars *approval* of ANDA or 505(b)(2) for 6 months
- Not a patent term extension so pre-commercial activities after patent expiration but before pediatric exclusivity expiration are not subject to damages or injunction
- In case of Para II and Para III (patent expiration), any exclusivity automatically begins at patent expiration
- Second Pediatric exclusivity available in some cases

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Part II: Major Controversies in the 30 Years Since the Enactment of Hatch-Waxman

30-Years of Hatch-Waxman: Lessons Learned

- 30-month stay of approval
- 180-day exclusivity and forfeiture issues
- Safe Harbor

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30-Month Stay of Approval

Issues Surrounding the 30-Month Stay of Approval

- Under original Hatch-Waxman Act
  - Filing of a lawsuit in response to a paragraph IV certification and notice letter triggered a 30-month stay of approval
  - A paragraph IV certification submitted to a patent listed in the Orange Book *after* the ANDA was filed resulted in a new 30-month stay
  - Allowed innovator company to obtain successive, multiple 30-month stays of approval with patent listing strategy

Issues Surrounding the 30-Month Stay of Approval

- 2002 FTC Generic Drug Study
  - http://www.ftc.gov/reports/generic-drug-entry-prior-patent-expiration-ftc-study
  - FTC concluded that:

"The 4 courts that have ruled so far on the patents causing more than one 30-month stay each have found the relevant patent to be invalid or not infringed. The other 4 drug products with multiple 30-month stays involved patents whose listing in the Orange Book could have been the subject of non-frivolous challenges by the generic applicant, had either FDA review of listability or a private right of action to challenge listability under Hatch-Waxman been available."

Issues Surrounding the 30-Month Stay of Approval

- 2002 FTC Generic Drug Study
  - http://www.ftc.gov/reports/generic-drug-entry-prior-patent-expiration-ftc-study
  - FTC concluded that:

"Multiple 30-month stays prevented FDA approval of the generic applicants' ANDAs for 4 to 40 months *beyond* the initial 30-month period. FDA approval may have occurred more quickly in the absence of the multiple 30-month stays, because the data indicate that FDA approval has occurred, on average, within 25 months and 15 days for generic applicants with paragraph IV certifications that were not sued."

Issues Surrounding the 30-Month Stay of Approval

- Medicare Prescription Drug and Modernization Act of 2003 (MMA)
  - Generally limits innovator to *one* 30-month stay for each ANDA product submitted with a paragraph IV certification
  - Patents listed in the Orange Book after the ANDA filed do not qualify for a 30-month stay
  - Multiple 30-month stays are still possible where changing ANDA product that results in a new paragraph IV certification
    - *E.g., Baxter Healthcare v. Minrad, Inc.* (desfluorane, USP)
  - Prevents innovator from using growing patent portfolio to unduly extending stay of FDA approval

Issues Surrounding the 30-Month Stay of Approval

- Extending 30-month Stay of Approval
  - Preliminary injunction preventing commercial launch
    - *E.g., Eisai Co. Ltd. v. Teva Pharmaceuticals* (donepezil) – FDA revoked final approval due to issuance of preliminary injunction
  - Failure to reasonably cooperate in expediting the litigation
    - "the [ANDA] approval shall be made effective upon the expiration of the [30-month stay] . . . ***or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action*** . . . ." FDC Act § 505(j)(5)(B)(iii) (emphasis added).
    - *E.g., Eli Lily & Co. v. Teva* (raloxifene HCl) – Court extended 30-month stay due to untimely change in ANDA product during litigation

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180-Day Exclusivity and Forfeiture

Issues Surrounding the 180-Day Exclusivity

- Under original Hatch-Waxman Act
  - 180-day exclusivity was determined on a patent-by-patent basis
  - ANDA applicants could be blocked beyond 180 days by exclusivity rights of first applicant with paragraph IV certification
  - ANDA applicants could share exclusivity as a result of “mutually blocking” exclusivities

Issues Surrounding the 180-Day Exclusivity

- 2002 FTC Generic Drug Study
  - http://www.ftc.gov/reports/generic-drug-entry-prior-patent-expiration-ftc-study
  - FTC concluded that:

"The data show that 14 of the 20 final settlements obtained through the study (discussed in Chapter 3) had the potential, at the time they were executed, to "park" the first generic applicant's 180-day exclusivity for some period of time, thus preventing FDA approval of any eligible subsequent applicants. In addition to the 20 final settlement agreements, there were 4 interim settlement agreements pursuant to which the patent litigation continued, but the parties agreed upon certain conditions in the meantime. The Commission, as noted above, has challenged interim settlements for 3 drug products."

Issues Surrounding the 180-Day Exclusivity

- Medicare Prescription Drug and Modernization Act of 2003
  - Created Forfeiture of Exclusivity
    - Failure to market ***by the later*** *of*:
      - The earlier of:
        - 75 days after approval of the application; or
        - 30-months after submission of the application;
      - OR 75 days after the date of:
        - An Appeals Court decision of invalidity or non-infringement of each relevant patent;
        - A settlement or consent decree entering a final judgment of invalidity or non-infringement of each relevant patent; or
        - Withdrawal of the patent listing

Issues Surrounding the 180-Day Exclusivity

- Medicare Prescription Drug and Modernization Act of 2003
  - Created Forfeiture of Exclusivity
    - *Other Forfeiture Events*:
      - Withdrawal of application of first applicant
      - Amendment or withdrawal of first applicant's certification for all patents
      - Failure to obtain tentative approval within 30 months
      - Violation of antitrust laws by virtue of a collusive agreement with another applicant, NDA holder, or patent owner
      - Expiration of all patents as to which first applicant submitted certification

      21 U.S.C. § 355(j)(5)(D)(i)

Issues Surrounding the 180-Day Exclusivity

- Medicare Prescription Drug and Modernization Act of 2003
  - Allowed Multiple "First Applicants"
    - 180-day exclusivity may be co-exclusive with other ANDA applicants who filed first

Issues Surrounding the 180-Day Exclusivity

- Continuing Issues Surrounding 180-Exclusivity
  - Delisting of Orange Book Patents does not trigger exclusivity
    - *Teva Pharmaceuticals USA, Inc. v. Sebelius* – Brand company could not trigger forfeiture event by unilaterally delisting Orange Book patent
  - Delay in amending certification cannot result in forfeiture of shared exclusivity
    - *Watson Labs. v. Sebelius* – FDA cannot deny 180-exclusivity to first-to-file applicant based on failure to ***amend*** certification at first opportunity
  - Reissue patent exclusivity not triggered by invalidity of surrendered patent but applicant must recertify

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Expanding Scope of Safe Harbor

What is the "Safe Harbor?"

- The Hatch-Waxman Act includes a provision that allows a generic drug company to conduct certain activities to **develop** its product without risk of patent infringement liability
  - *35 U.S.C. § 271(e)(1)*

- The "safe harbor" provides immunity from infringement liability for acts **reasonably related** to the development and submission of any information to the FDA, including the development of a generic drug application

Safe Harbor Overview

- 35 U.S.C. 271(e)(1):
  - "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 been varied regarding what activities are covered by the safe harbor.

Safe Harbor Issues & Questions

- When is R&D too early to be reasonably related to developing a drug for the FDA?
  - *Merck v. Integra Lifesciences*, Supreme Court (2005)
- What is a "research tool," and are they covered by the safe harbor?
  - *Proveris v. Innovasystems*, Federal Circuit (2008)
- Are process, testing or other patents used for commercial release testing "reasonably related" to FDA filings such that the activity falls within the safe harbor?
  - *Momenta v. Amphastar*, Federal Circuit (2012)

Merck v. Integra Lifesciences

Supreme Court (2005)

- Integra owned five patents related to its "RGD peptide" technology.
- Merck, without a license from Integra, used the "RGD peptide" technology to evaluate potential drug candidates.
- The Supreme Court held that the 271(e)(1) safe harbor did not exempt from infringement:
  1. Experimentation on drugs that are not ultimately the subject of an FDA submission
  2. Use of patented compounds in experiments that are not ultimately submitted to the FDA
- The Court interpreted the "reasonable relation" requirement of 271(e)(1) broadly in order to leave "adequate space for experimentation and failure on the road to regulatory approval."

Merck v. Integra Lifesciences

Supreme Court (2005)

- Despite the Court's broad interpretation of the 271(e)(1) safe harbor, the Court limited the circumstances in which it applied.
- "Basic scientific research" is not included in the safe harbor:
  - "Basic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce, is surely not "reasonably related to the development and submission of information" to the FDA."
- Researcher must have a "reasonable basis" that the patented technology will lead to an FDA submission:
  - Properly construed, § 271(e)(1) leaves adequate space for experimentation and failure on the road to regulatory approval: At least where a drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is "reasonably related" to the "development and submission of information under . . . Federal law." § 271(e)(1).

Proveris v. Innovasystems

Federal Circuit (2008)

- Innova made a device used to measure the physical parameters of aerosol sprays used in nasal spray delivery systems.
  - The product itself is not subject to FDA approval, but is used in connection with FDA regulatory submissions.
- Proveris sued Innova for using its patent technology in this device.
- The Federal Circuit held that because the "patented invention" is not subject to FDA approval, and therefore faces no barrier to entry upon patent expiration, the product is not within the category the safe harbor is designed to protect.
  - This case excluded "research tools" from the safe harbor.
- This case also emphasizes symmetry between 156(f) patent term extension and 271(e)(1) safe harbor protection

Momenta v. Amphastar

Federal Circuit (2012)

- Momenta owned a patent covering a method of analyzing a drug product (enoxaparin) that can be used to demonstrate to FDA that the generic drug is the same as the branded drug.
- Momenta sued Amphastar for using its patented method to collect data on Amphastar's generic enoxaparin.
  - The data generated from the patented method was not submitted to FDA, but collected and stored for each commercial batch, as required by FDA.
- The Federal Circuit held that Amphastar's post-FDA approval use of the patented method was covered by the safe harbor because Amphastar was required by FDA to maintain the data.
  - Amphastar's use was reasonably related to development and submission of information to the FDA, even after commercial launch.
- This case expands the safe harbor to some post-approval activities

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Questions?