Non-Patent Exclusivity

FDA Boot Camp, Boston
September 23, 2008

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Five Types of Non-Patent Exclusivity

- New Chemical Entity ("NCE") Exclusivity – 5 yrs
- New Clinical Study Exclusivity – 3 yrs
- Orphan Drug Exclusivity – 7 yrs
- Pediatric Exclusivity – 6 mos
- Generic Drug Exclusivity – 180 days

New Drug Applications

- **"Full" New Drug Application – 505(b)(1)**
  - Includes results of human clinical trials sufficient to prove safety and efficacy
- **505(b)(2) Application**
  - Relies, at least in part, on published information or FDA's past finding of safety and efficacy
  - Examples: new dosage form, strength, route of administration, dosing regimen, indication
- **Abbreviated New Drug Application – 505(j)**
  - Same active ingredient, dosage form, strength, route
  - Need prove only bioequivalence

NCE Exclusivity

- Hatch-Waxman Act, 1984
- Granted: to drug products containing a New Chemical Entity
- Blocks: submission of 505(b)(2) or ANDA
- Length: five years (or four years if para. IV)

- Statutes: 21 USC 355(c)(3)(E)(ii) – 505(b)(2)
  21 USC 355(j)(5)(F)(ii) – ANDA
- Regs: 21 CFR 314.108(b)(2)

“New Chemical Entity”

- **Definitions in 21 CFR 314.108(b)**
  - New Chemical Entity: “a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act”
  - Active Moiety: “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance”

NCE Exclusivity For Enantiomers?

- **Federal Drug Administration Amendments Act, 2007 ("FDAAA")**
- **Under strict conditions, an enantiomer can qualify as a NCE:**
  - The single enantiomer has not been previously approved except in the approved racemic drug
  - The NDA includes full new clinical investigations
  - The clinical studies were not used for the racemate
  - The enantiomer indication is not in the same therapeutic category as the racemate
- **Three-year exclusivity available: e.g., Lexapro (escitalopram); Nexium (esomeprazole)**

Extension of 30-Month Stay

- **P. IV ANDA or 505(b)(2) can be filed at "NCE -1" date**
- **If NDA holder/patent owner sues within 45 days, approval of ANDA/505(b)(2) is stayed for 30 months**
- **If suit filed within the one-year period beginning four years after NDA approval, the 30-month stay is extended by amount of time such that 7.5 years will elapse from the date of NDA approval**

New Clinical Study Exclusivity

- Hatch-Waxman Act, 1984
- Granted: for submission of results of new clinical studies
- Blocks: approval of 505(b)(2) or ANDA
- Length: three years

- Statutes: 21 USC 355(c)(3)(E)(iii, iv) – 505(b)(2)
  21 USC 355(j)(5)(F)(iii, iv) – ANDA
- Regs: 21 CFR 314.108(b)(4) and (5)

New Clinical Study Exclusivity

- **Granted for submission of "reports of new clinical investigations (other than biovailability studies) essential to the approval of the application [or the supplemental application] and conducted or sponsored by the applicant"**
- **Examples: new or changed formulations; salts; indications; dosing regimens; patient populations; OTC switches; or other label changes**
  - Opana ER (immediate release → extended release)
  - Caduet (atorvastatin/amlodipine combination)

New Clinical Study Exclusivity

- **Requirements – 21 CFR 314.108(a):**
  - Cannot apply to a new active moiety itself
  - Studies may not be bioequivalency or bioavailability studies
  - Studies must be conducted or sponsored by applicant
  - Studies must be new
    - results not relied on by FDA to demonstrate effectiveness of a previously approved drug product for any indication
  - Studies must be "essential to approval"
    - No other available data could support approval

BMS v. Shalala (D.C. Cir. 1996)

- **Capoten (captopril) originally indicated for hypertension**
- **Subsequently approved for (i) ventricular dysfunction and (ii) diabetic nephropathy**
  - 3-year exclusivity granted on both new indications
- **In general, generic drug label should be the same as the brand-name drug label**
- **However, under statute and regs, ANDA applicants can "carve out" certain indications from their labeling**
- **BMS sued FDA, arguing no ANDA can be approved as long as there is any three-year exclusivity**
- **Court held in favor of FDA**

Orphan Drug Exclusivity

- **Orphan Drug Act, 1983**
- **Granted: to drugs intended for treatment of a "rare disease or condition"**
  - Affects < 200,000 people in the U.S., or
  - No reasonable expectation of recouping dev. costs
- **Blocks: approval of 505(b)(1), (b)(2), or ANDA directed to the same drug, for same disease**
- **Length: seven years**
- **Additional rewards: tax credits; grants; fees waived**

- **Statute: 21 USC 360aa-dd**
- **Regs: 21 CFR 316**

Orphan Drug Exclusivity – Process

- **Apply for orphan drug status**
  - Upon designation, eligible for tax credits, grants, etc.
  - Added to list of orphan drug designations
- **Submit marketing application (NDA)**
  - Reviewed like other NDAs
  - Upon approval, added to Orange Book

“Celebrating the Success of the Orphan Drug Act”

- FDA Office of Orphan Products Development
- 300 treatments approved in past 25 years (only ten had been approved prior to the Act)
- FDA states there are 7,000 rare diseases or conditions
- 1700 drugs have been granted orphan drug status

Internet Break!

Pediatric Exclusivity

- Food and Drug Administration Modernization Act, 1997 ("FDAMA")
- Granted: to applicants who successfully complete FDA-requested clinical trials of a drug in a pediatric population
- Blocks: approval of 505(b)(2) or ANDA
- Length: six months beyond any existing marketing or patent exclusivity
- Also: gov't funding of ped studies if no exclusivity

- Statute: 21 USC 355A
- FDA Guidance: www.fda.gov/cder/guidance/2891fnl.htm

Pediatric Exclusivity – Process

- **FDA makes written request for pediatric studies, identifying a timeframe for completion**
  - Applicant may propose that FDA request the studies
- **NDA holder agrees to request, completes studies within timeframe, and submits acceptable reports**
- **"Acceptable reports":**
  - If FDA and sponsor agree on study protocol, completion in accordance with agreement sufficient
  - If no agreement, requirement met if reports fairly respond to written request, are conducted by accepted scientific principles, reported properly, etc.
- **Note: studies need not be successful**

Generic Drug Exclusivity

- **Hatch-Waxman Act, 1984**
- **Granted: to first ANDA applicant who submits a "substantially complete" ANDA containing a paragraph IV certification**
  - Substantially complete = sufficient to permit review
- **Blocks: approval of subsequently-filed <u>ANDA</u> containing a paragraph IV certification**
- **Length: 180 days, from commercial marketing**

- **Statute: 21 USC 355(j)(5)(B)(iv)**
- **FDA Guidance: www.fda.gov/cder/guidance/5710fnl.pdf**

180-Day Exclusivity Forfeiture

- **Medicare Modernization Act, 2003 ("MMA")**
- **Six ways to forfeit:**
  1. failure to market
  2. withdrawal of application
  3. amendment of certification
  4. failure to obtain tentative approval within 30 mos.
  5. improper agreement with another applicant, the listed drug application holder, or a patent owner
  6. expiration of all patents
- **Decided case by case:**
  – FDA considers forfeiture only when approval of a subsequent ANDA may be blocked by a first appl.

Norvasc Case: Pediatric/180-Day Exclusivity Interaction

- **Pfizer: U.S. Patent No. 4,879,303**
  - Claims amlodipine besylate
  - Expired 3/25/07 (pediatric excl. to 9/25/07)
- **ANDA Filers:**
  - Mylan (first filer/180-day excl. holder)
    - Pfizer did not sue w/in 45 days → no 30 mo. stay
    - Oct. 2005: FDA grants final approval
    - W.D. Pa. 3/16/07: ’303 valid and enforceable
  - Apotex
    - N.D. Ill. 1/29/06: ’303 valid and enforceable
  - Synthon
    - M.D.N.C. 8/31/06: ’303 valid and enforceable

Norvasc Case: Flurry of Activity

- March 22: Fed. Cir. invalidates '303 patent
- March 23: Mylan launches generic, triggering 180-day exclusivity period
- March 23: Pfizer launches authorized generic
- March 25: '303 patent expires
- March 26: Mylan files suit against FDA in D.C. district court, seeking to enjoin FDA from granting final approval to any other Norvasc® ANDAs
- March 26: FDA promises to seek views of interested parties; agrees to hold off until April 11
- March 26: District court enjoins FDA until April 13
- April 5: Pfizer files petition for rehearing or rehearing *en banc* of March 22 Fed. Cir. decision

Norvasc Case: FDA Decision, Apr. 18

(http://www.fda.gov/ohrms/dockets/dockets/07n0123/07n-0123-let0002-vol1.pdf)

1. All unapproved ANDAs are currently blocked by Pfizer's pediatric exclusivity
2. If and when the mandate effectuating the Fed. Cir. decision issues, Pfizer's pediatric exclusivity will not block final approval of Apotex's ANDA
3. FDA cannot determine on the current record whether other ANDAs will continue to be blocked by pediatric exclusivity at that time
4. Mylan's 180-day exclusivity terminated when the '303 patent expired (March 25)

Questions?

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