

Deciphering Section 505(b)(2) and Its Implications for Innovation and Patient Care

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Agenda

- Overview of Section 505(b)(2)
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- Strategic Opportunities
Jim Czaban
- Critique of FDA's Approach
Jeff Chasnow
- Questions and Comments
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Overview of Section 505(b)(2)

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Section 505(b)(2)

21 U.S.C. § 355(b)(2)

An application **submitted under paragraph (1)** for a drug for which the **investigations described in clause (A)** of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the **applicant has not obtained a right of reference** or use from the person by or for whom the investigations were conducted...

Section 505(b)(2)

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21 U.S.C. § 355(b)(1)(A)

[The applicant] shall submit to the Secretary as a part of the application...**full reports of investigations** which have been made to show whether or not such drug is safe for use and whether **such drug** is effective in use...

Marketing Applications: Post-1984

New Drug Applications (NDAs)

- *“Full Reports” of Safety and Efficacy Investigations*
- *Applicant has right of reference to essential investigations?*

YES

505(b)(1)

NO

505(b)(2)

Abbreviated New Drug Applications (ANDAs)

- *Duplicate of an already approved product*
- *No safety/efficacy data permitted (only bioequivalence)*

505(j)

505(b)(2): Historical Highlights

- Paper NDAs
- Hatch Waxman
- Parkman Letter
 - Phantom ANDA
- FDA Draft Guidance for Industry (1999)
- FDA Response to Citizen's Petition (2003)
- Follow-on Biologics

Key Concept in 505(b)(2): Reliance

- What is “Reliance”
 - By whom?
 - On what?
- Reliance and Exclusivity
 - Market vs. Data Exclusivity
 - Safety/Efficacy Data vs. CM&C data
- FDA Process for Determining Reliance
 - Who, when and how?

Strategic Opportunities And Public Health Benefits Using 505(b)(2) NDAs

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The “Big Picture”

- 505(b)(2), as interpreted by FDA, is a reality, and sponsors and FDA are using this pathway to offer the benefit of more therapeutic choices to patients and physicians.
- By definition, 505(b)(2) NDA products fill a gap in the pharmaceutical armamentarium, because identical (i.e., generic) products need to go through an ANDA. If innovators don't want to develop improved variations of existing drugs, how does it help patients to prevent others from doing so cost-effectively?
- 505(b)(2) NDAs are not a cakewalk, nor a windfall – they often require substantial additional innovative work to bring the product to market.

The “Big Picture”

- Patents are fully protected under 505(b)(2), because applicants must certify to listed patents on the reference drug, and patentees have at least 30 months to vindicate their patent(s) through litigation without competition.
- Unlike generics, 505(b)(2) products do not get “AB” ratings, so are not automatically substituted for original products.
- The safety/efficacy of approved products is a matter of public record, as reflected in the approved labeling. Forcing applicants to re-invent the wheel would be a costly and unnecessary policy choice.
- Indeed, it would be unethical to subject patients to clinical studies just to prove what everybody already knows about a drug.

Product Opportunities Under 505(b)(2)

- New Chemical Entity (rarely)
- New dosage form
- New dosing regimen
- New strength
- New route of administration
- New indication

Product Opportunities Under 505(b)(2)

- New active ingredient (different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of active moiety)
- New inactive ingredient that requires more than limited confirmatory studies
- Rx → OTC switch
- New Combination Products
- “Generic biologics”

Product Opportunities Under 505(b)(2)

Exclusivities available for 505(b)(2) products

- NCE Exclusivity (5 years)
- New Product Exclusivity (3 years)
- Orphan Drug Exclusivity (7 years)
- Pediatric exclusivity extensions (6 months)

Patent Issues

- 505(b)(2) drugs can have Orange Book-listed patents, and enjoy 30-month stay protection against generic competitors
- But, 505(b)(2) NDAs may also be blocked by patents on Reference Drugs

Enlarging the Pie for Patients*

- NCE
 - Thalomid® (thalidomide) (1998)
- Marketed unapproved drugs
 - Levothyroxine (2000)
 - Guaifenesin extended release (2002)
 - Quinine sulfate (2005)
- New Dosage Form
 - Tramadol orally disintegrating tablets (2005)
 - Ondansetron oral spray (filed 2006)

** Examples based on publicly available information*

Enlarging the Pie for Patients*

- New Dosing Regimen
 - Tramadol extended release tablets (2005)
- New Strength/Formulation
 - Antara (micronized fenofibrate caps) (2004)
(130 mg is BE to Tricor 200 mg)
- New Formulation/Inactive Ingredient
 - Avita (tretinoin gel) (new emollient) (1998)
 - Abraxane (cremaphor-free paclitaxel) (2005)
 - Oxy-ADF (oxycodone formulated to reduce drug abuse) (in development)

** Examples based on publicly available information*

Enlarging the Pie for Patients*

- New Active Ingredient
 - Pexeva (paroxetine mesylate) (new salt) (2003)
- New Route of Administration
 - Emezine (prochlorperazine) (new buccal/transmucosal delivery) (NDA pending)
 - Oral amphotericin-B (pre-clinical)
- Rx→OTC Switch
 - Alavert (loratadine) (2002)

** Examples based on publicly available information*

Enlarging the Pie for Patients*

- “Generic Biologics”
 - Omnitrope (rHGH) (2006)
 - Glucagen (glucagon recombinant) (1998)
 - Hyaluronidase (various approvals 2004-05)
 - Fortical (calcitonin salmon recombinant) (2005)

** Examples based on publicly available information*

Summary

- The 505(b)(2) train has left the station.
- Patients, companies (both small and large), and investors now depend on 505(b)(2) as an engine for medical innovation and improved patient care.
- Academical debate aside, Congress would not likely stand still for long if FDA's interpretation of 505(b)(2) were overturned.

Critique of FDA's Approach

Jeff Chasnow
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Section 505(b)(2): FDA's Misadventure

- FDA's Premise:
 - "Findings" from approval of NDA X may be used to facilitate approval of NDA ~X (modified version of product X) or even NDA Y if Y is "sufficiently similar" to X
- FDA's Logic:
 - Avoid "duplicative" or "unnecessary" studies
 - Conserve FDA review resources
 - Decrease drug costs
- FDA's Problem:
 - Hatch-Waxman law does not authorize this sort of short-cut
 - FDA tightropes across a clear legal prohibition on the use of proprietary NDA data
 - FDA's standardless approach is incompatible with essential statutory purposes

FDA's Tightroping: The Pit

- Before Hatch-Waxman, the law clearly prohibited FDA from using data within NDA X to support approval of NDA $\sim X$ (or NDA Y)
 - “[N]o data in an NDA can be utilized to support another NDA without express permission of the original NDA holder.”
[FDA “Finkel Memorandum” (1978, 1981)]
- Hatch-Waxman removed this barrier only for ANDAs
 - Expressly authorized ANDA approval without new safety/efficacy data, for identical/bioequivalent generics
 - ANDA process allows *“generic producer of the fully tested drug to rely on the safety and efficacy data of a prior applicant”*
Merck & Co., Inc. v. Kessler, 80 F.3d 1543, 1546 (Fed. Cir. 1996)
- 505(b)(2) does not authorize such data reliance
 - Merely sets conditions for certain NDAs
 - Requires “full reports of investigations” establishing safety and effectiveness [21 USC §§ 355(b)(1)(A), (d)(1)]

FDA's Tightroping: The Wire

- FDA constructs a false dichotomy between “findings” and data
 - Acknowledges that *“reliance on FDA’s finding of safety and effectiveness for a listed drug is indirect reliance on the data in a prior NDA”* [Omnitrope Response at 31]
 - But insists that such reliance is not improper use or disclosure of NDA data
- Under FDA’s construct, legality of reliance is a memory game
 - Reliance is ok if FDA remembers the fullness of its “findings” from an NDA
 - Reliance is illegal when review of the follow-on product requires reference to NDA documents
 - E.g. FDA suspended 505(b)(2) approval (amlodipine maleate) when *“A first line reviewer made reference to certain studies of Pfizer’s in the documentation of his review of [Reddy’s NDA]”*
[FDA Motion for Stay of Proceedings, No. 03-2346 (D.D.C. filed 2/18/04)]

505(b)(2) As An Unbounded ANDA

- ANDA: carefully circumscribed
 - Same active ingredient and labeling; bioequivalent product
 - Same dosage form, strength, route of administration
 - Slight modifications allowed under public process
- 505(b)(2) [FDA's view]: standardless
 - Allows a range of boundless product modifications, none of which is identified in Hatch-Waxman
 - Different active ingredient (including certain biologics)
 - Different indication
 - Different dosing regimen
 - Available whenever FDA determines "it is appropriate for the applicant to rely on the Agency's finding of safety and effectiveness for the listed drug." [Omnitrope Response at 6]
 - In other words: no legal standard, only a scientific standard

505(b)(2) Is Not An ANDA Without Bounds

- 505(b)(2) does not authorize FDA to avoid the limitations inherent in ANDAs
- Boundlessness has no place within the Hatch-Waxman scheme
 - Key goal of HW is to promote investments in R&D for new drugs
 - Impossible to promote investment if there's uncertainty
- HW's limits on generics are an essential part of the statute's dual purpose of enhancing innovation and facilitating generics
 - Innovation goals are not isolated in the exclusivity and patent-restoration provisions of HW, as FDA seems to suggest [Omnitrope Response at 4]
 - HW's twin goals infuse all aspects of the statute, and thus require strict textual construction (see recent decisions on "authorized generics")
- Also: it makes no sense to conceive of circumscribed ANDAs, but boundless 505(b)(2)s
 - Driver's license analogy

Summary of FDA's Misadventure

- FDA's tightrope, on the artificial construct of "findings," does not avoid legal restrictions on the use of NDA data in support of third-party applications
- FDA's unbounded interpretation of 505(b)(2) is unsupported by the statute, and incompatible with the statute's fundamental purposes
 - Policymaking venture that goes beyond HW
 - Similar to efforts on 180-day exclusivity that courts have rejected
- FDA's approach, in my view, will be difficult to sustain against an appropriate judicial challenge

References

References

- 21 U.S.C. § 355(b)(2) *et seq.*
- 21 C.F.R. § 314.54 *et seq.*
- Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, CDER and CBER, FDA, May 1998
- [draft] Guidance for Industry, *Applications Covered by Section 505(b)(2)*, CDER, FDA, October 1999
- FDA Response to Citizen's Petition of Pfizer Inc., May 30, 2006, Docket Nos. 2004-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1 and 2004N-0355
- FDA Response to Citizen's Petition of Pfizer, Inc. and BIO, October 14, 2003, Docket Nos. 2001P-0323/CP1 and C5, 2002P-0447/CP1 and 2003P-0408/CP1
- FDA response to Citizen Petition on recombinant Salmon Calcitonin, Aug. 12, 2005, Docket No. 2004P-0015.
- FDA's Omnitrope information pages
(<http://www.fda.gov/cder/drug/infopage/somatropin/default.htm>)