The Abbreviated New Drug Application (ANDA), 505(b)(2) Applications, and Patent/Exclusivity Issues

Introduction to Drug Law and Regulation
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Komal Karnik Nigam
Hogan Lovells US LLP

FDLI

Learning Objectives

- Generic drug approval pathway and requirements of sameness, bioequivalence, and therapeutic equivalence
- Patent listing and certification requirements, and implications for Hatch-Waxman patent infringement cases
- Eligibility requirements and scope of market exclusivities for innovator and generic products

Abbreviated New Drug Applications

- Eligibility for ANDA Consideration
  - Orange Book
  - Suitability Petitions
- Content and Organization of an ANDA
- Sameness, Bioequivalence and Therapeutic Equivalence

The Drug Price Competition and Patent Term Restoration Act of 1984

- **“Hatch-Waxman Amendments”**
- Intended to increase the availability of low cost generics while preserving the incentive to innovate
- Title I
  - Authorized generic sponsors to rely on pioneers’ data
  - Provided pioneers with exclusivity to preserve incentive
- Title II
  - Authorized patent term extensions
  - Allowed for early (i.e., pre-ANDA approval) litigation of patents

The Orange Book

- *"Approved Drug Products with Therapeutic Equivalence Evaluations"*
- Identifies drug products approved by FDA that have not been withdrawn for safety or efficacy reasons
- Sorted by active ingredient, dosage form, route of administration, strength
- 1+ reference listed drugs (RLDs) identified for each category
  - Also identifies reference standards, which represent FDA's judgment about the appropriate comparator for conducting any *in vivo* bioequivalence studies
- Therapeutic equivalence (TE) rating assigned for "multisource" drugs
  - TE = PE + BE
- Preface, patent listings and exclusivity dates, use codes

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search Results for Proprietary Name, Active Ingredient or Application Number: *aripiprazole*

RX OTC DISCN

CSV Excel Print

Display 50 records per page

Showing 1 to 50 of 144 entries

Search for text in the table

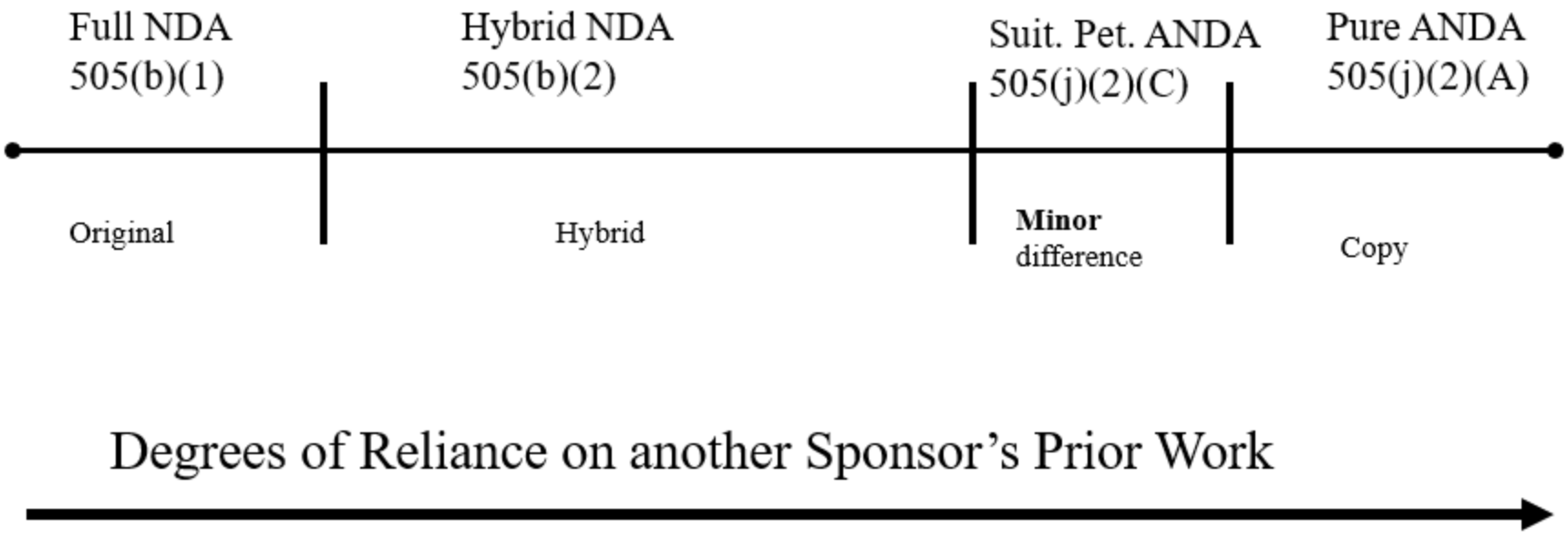
Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ARIPIPRAZOLE	ABILIFY MAINTENA KIT	N202971	FOR SUSPENSION, EXTENDED RELEASE	INTRAMUSCULAR	300MG/VIAL		RLD		OTSUKA PHARMACEUTICAL CO LTD
RX	ARIPIPRAZOLE	ABILIFY MAINTENA KIT	N202971	FOR SUSPENSION, EXTENDED RELEASE	INTRAMUSCULAR	300MG		RLD		OTSUKA PHARMACEUTICAL CO LTD
RX	ARIPIPRAZOLE	ABILIFY MAINTENA KIT	N202971	FOR SUSPENSION, EXTENDED RELEASE	INTRAMUSCULAR	400MG/VIAL		RLD	RS	OTSUKA PHARMACEUTICAL CO LTD
RX	ARIPIPRAZOLE	ABILIFY MAINTENA KIT	N202971	FOR SUSPENSION, EXTENDED RELEASE	INTRAMUSCULAR	400MG		RLD		OTSUKA PHARMACEUTICAL CO LTD
RX	ARIPIPRAZOLE	ARIPIPRAZOLE	A203906	SOLUTION	ORAL	1MG/ML	AA		RS	AMNEAL PHARMACEUTICALS
RX	ARIPIPRAZOLE	ARIPIPRAZOLE	A204094	SOLUTION	ORAL	1MG/ML	AA			APOTEX INC

Patent and Exclusivity for: N202971

Product 001
ARIPIPRAZOLE (ABILIFY MAINTENA KIT) FOR SUSPENSION, EXTENDED RELEASE 300MG/VIAL

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	7807680	10/19/2024		DP			
001	8030313	10/19/2024			U-543 U-1632		
001	8338427	03/15/2025		DP	U-543 U-1633		
001	8338428	08/06/2023		DP	U-543 U-1633		
001	8399469	06/29/2025	DS				04/15/2013
001	8722679	10/19/2024		DP			06/09/2014
001	8759351	08/06/2023		DP	U-1530 U-1633		07/22/2014
001	8993761	09/25/2022	DS				04/28/2015
001	9089567	01/28/2022			U-543		08/26/2015
001	10525057	03/08/2034			U-543 U-1632 U-2723		01/31/2020


Full NDA
505(b)(1)
Hybrid NDA
505(b)(2)
Suit. Pet. ANDA
505(j)(2)(C)
Pure ANDA
505(j)(2)(A)
Original
Hybrid
Minor
difference
Copy
Degrees of Reliance on another Sponsor's Prior Work

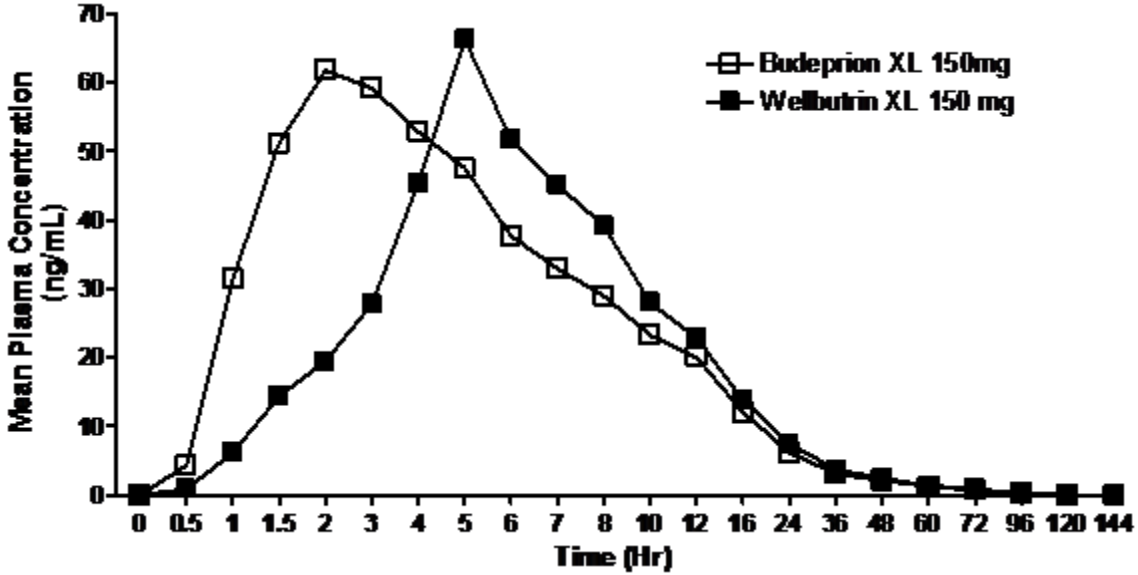
ANDA Requirements

- An ANDA is a type of NDA that does not contain complete reports of safety and effectiveness
- Under 21 USC 355(j), ANDA applicants can rely, for approval, on a previously approved “reference listed drug” (RLD) if the applicant shows:
  - “Sameness” (with respect to active ingredient(s), dosage form, route of administration, and strength)
  - Bioequivalence
  - Same conditions of use/Same labeling (with certain exceptions)
- In exchange for reliance, the ANDA applicant will also be subject to the RLD’s patents and exclusivities

Bioequivalence

- No significant difference in the rate and extent to which the drug is absorbed and becomes available at the site of action
- For systemic drugs, typically shown through single dose crossover study in healthy subjects based on pharmacokinetic measures under fed and fasted conditions
  - Maximum concentration (Cmax), which reflects the *rate* of absorption
  - Total concentration from dosing until last measured time point (AUCt) and extrapolated out until infinity (AUCinf), which reflects the *extent* of absorption
  - The 90% confidence interval of Cmax, AUCt, and AUCinf (not Tmax) of the test-to-reference ratio must fit within 0.80 and 1.25

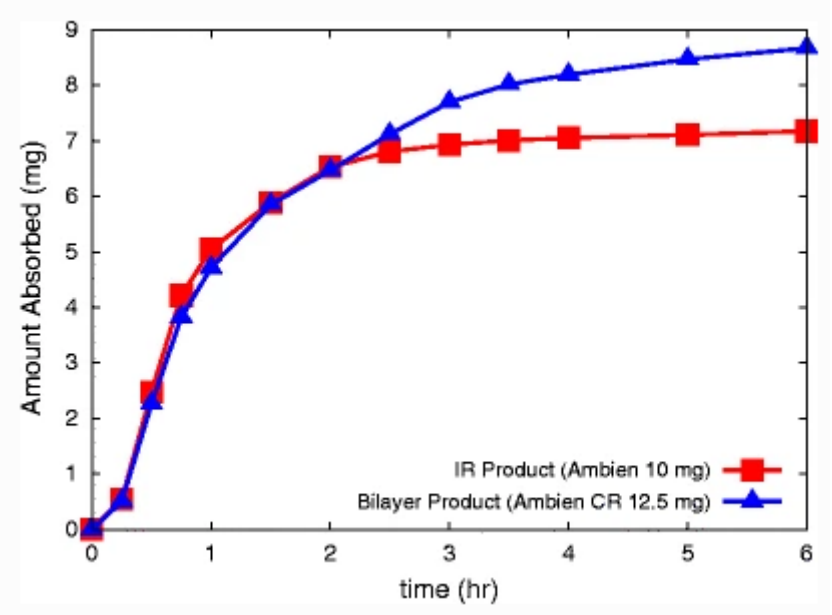
Generic Bupropion XL: Are AUC and Cmax Enough?



- Based on Cmax and AUC, FDA held that these two drugs, at the study strength of 150 mg, are bioequivalent
- Further, BE was automatically established for the higher strength, 300 mg dose, based on a ‘bio-waiver”

“Third” PK Parameters in Select Cases

- For some multiphasic, modified-release drug products, FDA has accepted the need for “partial” AUC metrics to ensure BE
  - Ambien CR (extended release zolpidem tartate) (2010)
  - Concerta (extended release methylphenidate HCl) (2012)
  - Metadate CD (extended release methylphenidate HCl) (2012)
  - Adderall (extended release amphetamine salts) (2012)
- Key elements in FDA’s partial AUC analysis
  - PK profile shows clinically relevant time intervals not adequately measured by the conventional PK parameter



BE for locally-acting products

- For non-systemically absorbed, locally-acting drugs, FDA has relied on alternative means of determining BE - usually a clinical study designed to assess non-inferiority of the proposed generic
  - Creams and ointments
  - Locally-acting gastrointestinal products
  - Certain inhalation products
- FDA is actively seeking in vitro and analytical methods, in place of clinical studies, to show BE for these products

Formulation Issues

- The inactive ingredients used, and the composition of the drug, cannot be “unsafe” under the labeled conditions of use
- Most dosage forms can and will have different formulations (e.g., to avoid a patent)
- Some dosage forms, however, are generally required to be “Q1” and “Q2” equivalent (e.g., injectables, ophthalmics, topicals)

Same Labeling Requirement

- ANDA must contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]" (same labeling requirement)
- BUT it does not require that an ANDA be approved for each condition of use for which the RLD is approved
- The FDCA further permits differences in labeling that may result because the generic drug product and RLD are produced or distributed by different manufacturers
  - Generics can "carve out" indications or other labeling protected by patent or exclusivity
- Examples of permissible differences include:
  - "… differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions … other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the [FDCA]." 21 CFR 314.94(a)(8)(iv).
  - Or indication protected by orphan exclusivity

Labeling “Carve Out”

- FDA will generally permit omission of an indication protected by patent or exclusivity unless the differences “***render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use***.” FDA has affirmed its authority to approve generic drug products with labeling that omits protected information on many occasions
- There are very few examples of FDA denying carve outs

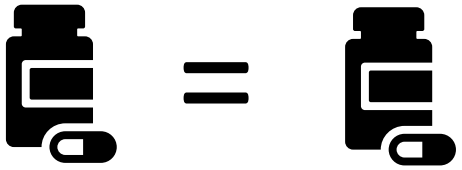
How does FDA evaluate carve outs?

- The agency does not look at the claims of the patent
- Ensures that the ANDA labeling does not “disclose” the protected use
  - “Selective deletions
  - De minimis modifications in the labeling
  - Alterations to Warnings, Adverse Event tables, Medication Guides, descriptions of clinical studies, have been permitted

Suitability Petitions

- The statute allows ANDAs to contain certain differences from RLDs in …
  - Active ingredient (combinations only)
  - Dosage form/route of administration
  - Strength
- …unless “investigations must be conducted” to show safety and effectiveness or extensive labeling changes would be required (505(j)(2)(C), 21 CFR 314.93)
- Petitions are available for public comment
- Approved product cannot be “AB” rated
- Subject to the Pediatric Research Equity Act (clinical studies may be required)

Authorized Generics



- Pharmaceutical originally marketed by a brand company, but licensed to a generic or relabeled and marketed under a generic product name by the brand company
- Used to settle generic litigation, get a head start in the generic market, and/or maintain market share

GDUFA

- FDARA reauthorized the Generic Drug User Fee Amendments (GDUFA) through Sep. 2022
- User fee rates (FY 2021):
  - E.g., ANDA: $196,868
- “Commitment letter” outlines goals for reviewing and acting on ANDAs and ANDA amendments
  - E.g., 90% of standard original ANDAs within 10 months of submission date

505(b)(2) Applications

- In practice, a 505(b)(2) NDA permits reliance for approval on published literature or on FDA's previous finding of safety and/or effectiveness for a "listed drug," i.e., a previously approved drug product.
  - Published literature: Any of the specific information necessary for approval (e.g., clinical trials, animal studies) that is obtained from literature or from another source to which the applicant does not have a right of reference.
  - Listed drug: Permits modification of a drug by reliance on FDA's previous finding of safety and effectiveness to the extent such reliance would be permitted for ANDA approval

505(b)(2) NDA Pathway

- Similar to a 505(b)(1) or “full” new drug application (NDA), a 505(b)(2) applicant must demonstrate safety and effectiveness through clinical data.
- Unlike a 505(b)(1) NDA, a 505(b)(2) applicant may rely on data from investigations not conducted by the applicant and for which the applicant does not have a right of reference. See 21 USC 355(b)(1) and (b)(2).
  - The “right of reference or use” is authority to rely on or use an investigation to seek approval, including the ability to make the underlying raw data available to FDA. 21 CFR 314.3(b).

505(b)(2) NDA Pathway

- Unlike an ANDA, cannot be approved on the basis of sameness and bioequivalence to listed drug
  - Rather, typically includes comparative BA data to bridge between the product and listed drug, and studies needed to support modifications
  - Also, need not be a duplicate of the listed drug
- Similar to an ANDA, relies to some extent on FDA's previous finding of safety and effectiveness for a listed drug

505(b)(2): Listed Drug

- Must identify a drug product as the "listed drug" if application relies on FDA's previous finding of safety or effectiveness for the product
  - Listed drug: A product that has current approval (i.e., FDA has not withdrawn or suspended the approval), and that "has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." 21 CFR 314.3(b)
- Cannot rely on an ANDA because there has been no previous finding of safety and effectiveness
- Unlike an ANDA, may identify and rely upon multiple listed drugs
  - If there is a pharmaceutical equivalent, generally must be identified as a LD
- Consequence of identifying listed drug similar to ANDAs: patent certification requirements

Patent Provisions

- Patent Listing
- Patent Certifications
  - Paragraph I, II, III, IV Certifications
  - Notice of PIV Certification
  - Challenges to Patent Listings
- 30-Month Stays on ANDAs and 505(b)(2) Approval

Patent Listing in the Orange Book

- NDA sponsors must submit to FDA "information" on patents that claim the drug, or an approved method of using the drug, and for which a claim of patent infringement could "reasonably be asserted"
  - Drug substance – active ingredient patents
    - Polymorph patents if applicant certifies to the existence of data demonstrating "sameness" to drug described in NDA
    - **NOT** patents that only claim intermediates or metabolites, or different salts or esters
  - Drug product – formulation and dosage form patents
    - **NOT** process or packaging patents
    - Device patents if considered integral to the dosage form of the drug, *e.g.*, metered-dose inhaler
    - "Product-by-process" patents only if the product is novel
- FDA defers to the sponsor on patent listings ("purely ministerial")

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
[illegible]
See OMB Statement on last page.

NDA Number
876543

Name of NDA Holder

Drug Pharmaceuticals

Refer to instruction sheet (FORM FDA 3542 SUPPLEMENT) for more information.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Active Ingredient(s)

CALCIPHEROUS CHLORIDE; METHYLDEXTROSE; MAGNACIFEROUS HYDROCHLORIDE; GLUTATIONEOXIDE; PENTYLHEXADYL CHLORIDE; SODIUM BIHEXYLNATE; SODIUM HYDROCHLORIDE; SODIUM PENTYLPHOSPHATE; TRIHEXIDINE HYDROCHLORIDE

Trade Name

Lettdrug

Strength(s) *(Include applicable Product Number, if available - See instructions)*

0.255MCG/ML;0.392MCG/ML;0.42MCG/ML;0.384MCG/ML;0.378MCG/ML;23.1MCG/ML;75.14MCG/ML;1.42MCG/ML

Dosage Form(s)	Route(s) of Administration	Type of Use
Tablets	Oral	☒ Prescription ☐ Over-the-Counter

Timing of Patent Listing

- Patents are required to be listed preliminarily with original application, followed by a formal listing within 30 days after approval
  - **OR**: 30 days after patent issuance, for later-issued patents
- In practice, failure to timely list patents means that FDA will not require pending ANDA applicants to "certify" to those patents
  - Pending applicants are required to certify to timely listed patents, but not "late listed" patents
  - Future applicants are nevertheless required to certify to "late listed" patents

Patent Listing: Use Codes

- Method of use patents must be listed with **240-character description**, *i.e.*, **"use code,"** which "must describe only the approved method(s) of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product"
  - FDA specifically requires that "[i]f the method(s) of use claimed by the patent does not cover an indication or other approved condition of use ***in its entirety***, the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted..." (emphasis added)
- NDA holder must identify the section(s) and subsection(s) of the approved labeling that describes the method(s) of use claimed by the patent submitted

Challenges to Patent Listings

- Previously, FDA would only request the NDA holder confirm the correctness of a use code listing
- On Oct. 6, 2016, FDA revised its regulations, including the process by which a challenger could dispute an Orange Book patent listing
- The rule was intended to address the issue of “overbroad use codes,” where the patent was narrower than the use code, such that a labeling carve out would have been viable if the use code had been described more precisely to correspond to the scope of the patent

Use Code Listing Dispute

Challenger notifies FDA with a statement of dispute with specific grounds for disagreement regarding the accuracy or relevance of patent information. For use code dispute, this must be only a narrative description (no more than 250 words) of the person's interpretation of the scope of the patent

↓

FDA sends this text to the NDA holder without review or redaction

↓

For a use code dispute, NDA holder must, within 30 days of the Agency sending the statement of dispute:

(1) Confirm the correctness of the use code or withdraw or amend the patent information

(2) Provide a narrative description (no more than 250 words) of its interpretation of the scope of the patent that explains why the existing or amended use code describes only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted

(3) Include a signed verification as described in the regulation

Use Code Listing Dispute

FDA will not change the patent information if it is confirmed by the NDA holder. FDA will amend the Orange Book if the NDA holder amends the patent information

FDA will "promptly" post information on its website regarding whether a patent listing dispute has been submitted for a particular use code and whether the NDA holder has timely responded to the patent listing dispute

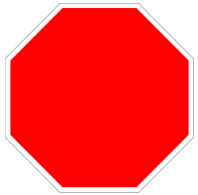
Patent Certification Requirements

- ANDA and 505(b)(2) applicants must certify to all patents listed in Orange Book with the drugs on which they rely
  - Paragraph I: No patent listed
  - Paragraph II: Patent has expired
  - Paragraph III: Patent will expire in future
  - Paragraph IV: Patent is invalid or will not be infringed or
  - Statement that the patent does not claim a use for which the ANDA applicant is seeking approval (method of use patent) – “section viii statement”
- With Paragraph I or II, FDA will approve when eligible
- With Paragraph III, FDA will approve upon patent expiry

Paragraph IV Certification Notice

- An applicant submitting a paragraph IV certification is required to give notice of the patent challenge to the holder of the NDA for the RLD and each owner of the patent that is the subject of the certification
  - Timing of notice: Within 20 days of "receipt" of ANDA. For amendments to ANDAs, notifications made at same time as certifications
- Submission of application with PIV certification an "artificial act of patent infringement," allowing for early litigation of patent disputes

30 Month Stay



- In most cases, if the NDA holder or patent owner initiates a patent infringement action within 45 days after receiving notice of the paragraph IV certification, there will be a statutory 30-month stay of approval of the ANDA while the patent infringement litigation is pending
  - The stay is immediately terminated upon a district court decision of invalidity or non-infringement of the patent or a settlement containing such a finding

Section viii Statement

- An ANDA applicant seeking to omit an approved method of use covered by a listed patent need not file a paragraph III or IV certification for that patent
  - An ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement (except for “split” certification)
  - If the labeling does not include an indication approved for the RLD, only the section viii statement is appropriate
- Instead, the applicant must submit a “section viii statement” acknowledging that a given method of use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval

Section viii Statement

- The statement requires the ANDA applicant to omit or "carve out" from its labeling, information pertaining to the protected use
- If an ANDA applicant files a section viii statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.
- Section viii statements also ***do not***
  - give rise to – and are not blocked by – 180-day exclusivity
  - require notice to the NDA or patent holder
  - give rise to 30-month regulatory stays

Marketing Exclusivity

- New Chemical Entity (5-Year) Exclusivity
- 3-Year Exclusivity
- Pediatric and Orphan Drug Exclusivities
- 180-Day Exclusivity
- 180-Day Competitive Generic Therapy Exclusivity

5-Year NCE Exclusivity

- Approval of a new chemical entity (NCE) means FDA is prohibited from approving ANDAs/505(b)(2) applications for the same drug for any use for five years from the date of approval of the NCE
- NCE means a drug that does not contain an active ingredient (including any salt or ester thereof) found in any other approved product
- The “active moiety” test – FDA looks at the molecule, stripped of any salts, esters, or other derivatives

5-Year NCE Exclusivity

- ANDAs/505(b)(2)s may not be submitted for 5 years, providing 6-7 years of protection
- The period is shortened to 4 years for ANDAs/505(b)(2)s that contain a PIV Certification
- Can be avoided by submitting a 505(b)(1) application, which is not blocked by the exclusivity
- Covers the entire NCE franchise – any indication, any strength, any dosage form

3-Year Exclusivity

- Three-year exclusivity blocks the approval (not submission) of ANDAs and 505(b)(2) products with the same “conditions of approval”
  - Does not block approval of a 505(b)(1)
- To qualify, an application or supplement must contain “reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant.” 21 USC(c)(3)(E)(iii), (iv) and (j)(5)(F)(iii), (iv)
  - New clinical investigations
  - Essential to the approval
  - Conducted or sponsored by the applicant
- FDA determines eligibility only at the time of approval

3-Year Exclusivity

- **New clinical investigation:** "an investigation in humans [(other than a bioavailability study)] the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product"
- **Essential to approval:** "there are no other data available that could support approval of the application."
- **Conducted or sponsored by:** "before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation."

Scope of 3-Year Exclusivity

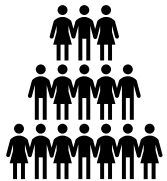
- If FDA approves an NDA "for a drug…" and if such application earns three-year exclusivity, the agency may not approve an ANDA or 505(b)(2) application "for the conditions of approval of such drug in the approved [NDA] ... before the expiration of three years from the date of the approval of the application."
  - "Conditions of approval" is not defined by statute or regulation
  - Slightly different language for sNDAs: "…for a change approved in the supplement…"
    - FDA interprets to mean "conditions of approval"
    - Not all changes made in supplement qualify for exclusivity. Zeneca Inc. v. Shalala; AstraZeneca Pharm. LP v. FDA

3-Year Exclusivity

- Unlike 5-Year NCE exclusivity, FDA may accept and review ANDAs/505(b)(2)s during the 3-year period
- Can be avoided by submitting a 505(b)(1) NDA
- Creates difficult issues in context of 505(b)(2) NDAs
  - Astagraf XL v. Envarsus XR
  - Abilify Maintena v. Aristada

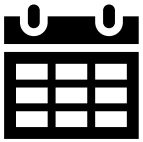
Orphan Drug Exclusivity

- For drugs intended to treat rare diseases
  - Fewer than 200,000 patients, or plausible subset
  - Request designation prior to submitting NDA
  - Obtain NDA approval
- FDA is prohibited from approving the “same drug” for the same disease or condition for 7 years
- Blocks ANDAs, 505(b)(1)s, and 505(b)(2)s
- The only way to avoid it is to create a different drug or to show “clinical superiority”



Pediatric Exclusivity

- Six month extension to all of sponsor's patents and exclusivities listed in Orange Book with relevant active moiety
  - Except, if a generic has PIV'd to a patent, 6 months is added on only if the innovator wins its patent case against the generic
- Applicant must "fairly respond" to an FDA written request for a pediatric study and submit results within timeframe; study need not have been successful
- Under 2007 FDA Amendments Act, pediatric study must be submitted at least 9 months before patent or exclusivity expiry *and probably should be submitted 15 months before expiry*



180-Day Generic Exclusivity

- Incentive for ANDA applicants to challenge pioneer patents
- First ANDA(s) with a PIV certification receives “180-day exclusivity”
- Triggered by the first commercial marketing of the drug
- Single period of exclusivity is awarded to the first applicant with a PIV to any listed patent
- All PIV applicants submitted on same day share exclusivity
- Numerous exclusivity forfeiture provisions, intended to prevent first generic from creating bottleneck

Competitive Generic Therapy Exclusivity

- Created by FDARA
- 180-day exclusivity for first ANDA approved
  - for a drug designated as a “CGT”
  - for which there were no unexpired patents or exclusivities listed in the Orange Book for the RLD when the ANDA was submitted and
  - That is commercially marketed within 75 calendar days after approval of the ANDA

Patent Term Restoration/Extension

- Restores portion of patent term lost to testing and FDA review (35 USC 156)
  - ½ the testing period + the FDA review period
  - 5 year maximum, and extension cannot cause patent life to exceed 14 years from approval
- Must apply to PTO within 60 days of approval
- Use on best patent – usually composition of matter
- Only available for first permitted commercial marketing of the "product" . . .
- which is defined to mean "active ingredient" . . . which may or may not be the same as an FDA-recognized "active moiety"

Thank you! Questions?

Komal Karnik Nigam
Senior Associate, Washington, DC
T 202-637-4883
Komal.Nigam@hoganlovells.com