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Orange Book Patent Listing

Best Practices and Current Challenges

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George works with life sciences companies of all sizes to assist them in developing and marketing innovative products that are regulated by the US Food and Drug Administration, including drugs and biologics, medical devices, drug-device combination products, CBD and botanical products, medical foods and dietary supplements.

George has deep experience providing regulatory advice to pharmaceutical and biotech companies on lifecycle management issues, including regulatory exclusivities and FDA-facing patent issues. He is a leading expert on orphan drug matters, including orphan designation and exclusivity, and has successfully advocated on behalf of clients to FDA on matters related to prevalence, orphan subsets, and clinical superiority. George also regularly advises pharmaceutical and biotechnology companies on pediatric study and pediatric exclusivity issues arising under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

Introduction

- Welcome to Mayer Brown's FDA Lifecycle Management webinar series
  - Monthly installments addressing issues affecting lifecycle of pharma and biotech products
  - Today's webinar addresses *Orange Book* Patent Listing
- Next installments will take place in the fall and cover additional regulatory issues
  - Recommendations or suggestions?

Today's Agenda

Patent Listing Basics

- Who? What? When? and How?

FDA's Role in Patent Listing

Implications of Patent Listing

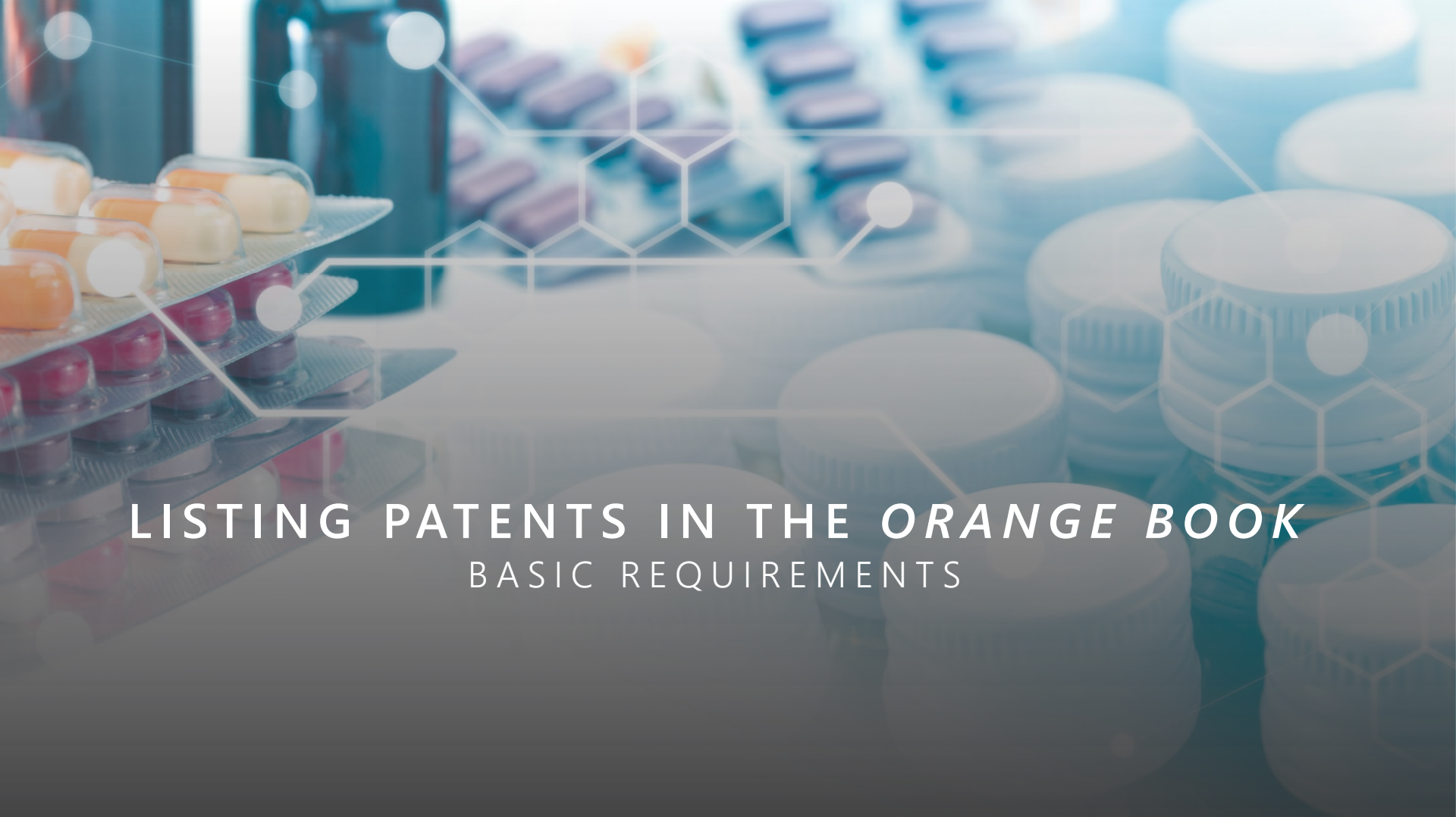
Filling out Form FDA 3542: Section by Section

Enforcement and Other Challenges

- Caselaw on REMS and Device Patents

Special Topics

- Pediatric Exclusivity
- Patent Listing for BLAs



LISTING PATENTS IN THE *ORANGE BOOK*

BASIC REQUIREMENTS

Patent Listing Basics

- What triggers obligation to submit patent information?
  - Submission of an NDA and certain sNDAs; not for BLAs, with one exception
- Which patents can (and therefore must) be submitted?
  - Patents claiming the Drug Substance, Drug Product or approved Method of Use
- How is information submitted?
  - Form FDA 3542a – at the time of application submission
  - Form FDA 3542 – within 30 days of application approval or within 30 days of patent issuance after application approval
- What does FDA do with this information?
  - Ministerial role: publishes information in the Orange Book

What triggers obligation to submit patent information?

- Submission of an NDA
- Submission of an sNDA that seeks approval to:
  - Add or change the dosage form or route of administration;
  - Add or change the strength; or
  - Change the drug product from prescription use to over-the-counter use, or
- For an sNDA seeking any other change, the
  - Submit any new patents that cover the changes approved in the sNDA
  - Submit forms for any patents whose Use Code(s) will be changing
    - Generally don't have to re-submit any previously listed patents; can, but not required to re-submit forms for other patents
  - Delist any patents that no longer cover the changed product

Which patents can and must be submitted?

- Each 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, and that—
  - (I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or
  - (II) claims a method of using such drug for which approval is sought or has been granted in the application"
- Three categories of patents and patent claims:
  - Drug Substance (DS), Drug Product (DP), and Method of Use (MOU) patents
- NOT: Manufacturing or process patents, patents claiming packaging, metabolites or intermediates

Drug Substance (active ingredient) patents

- Typically, these are compound or composition of matter claims
  - "A compound having the structure … or a pharmaceutically acceptable salt…"
  - Can cover the active moiety (abacavir) or the active ingredient (abacavir sulfate)
- Polymorphs: if the drug substance is in one polymorphic form, patents claiming that form can and must be listed, even if they claim other polymorphic forms
  - If the patent claims only a different polymorphic form, it can and must be listed if the applicant certifies to FDA that the applicant has "test data" demonstrating that drug product with patented polymorph will perform the same way as approved NDA
  - Regulations describe test data in more detail
- Not metabolites or intermediates

Drug Product (formulation and composition) patents

- Typically, these are patents claiming the formulation
  - "a composition comprising the compound of claim 1 and a pharmaceutically effective excipient…"
  - The active ingredient with inactive ingredients/excipients, or
  - The active ingredient in a dosage form/route of administration
- Drug product is defined by regulation to mean "a finished dosage form, *e.g.*, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients"
- Product-by-process: permitted, but quite rare

Method of Use patents

- Methods of using the drug
  - "A method of treatment comprising administering a therapeutically effective amount of compound X…"
  - "A method of administering…"
- Only patents that claim indications or other conditions of use described in the FDA-approved labeling
- In 2016 rulemaking, FDA tried to tighten up the drafting of Use Codes:
  - "If 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 if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product." 81 FR 69598 (Oct. 6, 2016)

How is patent information submitted?

- For existing patents, a two-stage process:
  - Stage 1: At the time of submission of an NDA or sNDA, by means of separate Form FDA 3542a for each patent
  - Stage 2: Within 30 days of approval, the information must be submitted again on Form FDA 3542
- For patents that issue while application is pending:
  - Submit 3542a within 30 days
- For patents that issue after application is approved:
  - Submit 3542 within 30 days
- Submission of forms is done as electronic submission to application
  - Not to Orange Book staff; cover letter: "TIME SENSITIVE PATENT INFORMATION"

The Agency's Role: What does FDA do with this information?

- "Ministerial" role
  - FDA relies on the NDA holder's statements in the 3542 form
- Publication in the Orange Book
  - Patent number and expiration date
  - Identify whether patent claims the drug substance, drug product and/or method of use
  - If method of use patent, a Use Code
  - Date of submission (post-2013)
  - Whether delisting request has been received

What does FDA do with this information? Sample Orange Book Listing

Patent and Exclusivity for: N205834

Product 001
LEDIPASVIR; SOFOSBUVIR (HARVONI) TABLET 90MG;400MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	7964580	03/26/2029	DS	DP	U-1470		10/30/2014
001	7964580*PED	09/26/2029					
001	8088368	05/12/2030	DS	DP			10/30/2014
001	8088368*PED	11/12/2030					
001	8273341	05/12/2030			U-1470		10/30/2014
001	8273341*PED	11/12/2030					
001	8334270	03/21/2028	DS	DP	U-1470		10/30/2014
001	8334270*PED	09/21/2028					
001	8580765	03/21/2028	DS	DP	U-1470		10/30/2014
001	8580765*PED	09/21/2028					
001	8618076	12/11/2030	DS	DP	U-1470		10/30/2014
001	8618076*PED	06/11/2031					

What does FDA do with this information?

- Timing
  - Patents are considered submitted when FDA receives the information, even if not yet published in Orange Book
  - For patent forms submitted with application, information is published after approval (generally Orange Book is updated by the end of second week of following month)
  - For patents that issue after approval, part of daily Orange book update
- Miscellaneous Procedures
  - If FDA notifies NDA holder that Form FDA 3542 is incomplete or has an error, the NDA holder must submit an acceptable Form FDA 3542 within 15 days of FDA's notification to be considered timely filed as of the date of the original submission of patent information

IMPLICATIONS OF LISTING PATENTS

Implications of Patent Listing

- Patent certifications: ANDA that seeks to rely on an approved drug as the "reference listed drug" (RLD) must certify to each listed patent or submit a "section viii statement"
- Four types of certifications
  - Paragraph I – patent information has not been filed
  - Paragraph II – listed patent has expired
  - Paragraph III – applicant will wait until patent has expired before receiving final approval
  - Paragraph IV – applicant believes patent is invalid or will not be infringed
    - Statement of no relevant patents under 21 CFR 314.50(i)(1)(ii), if there are no patents listed in the Orange Book

Implications of Patent Listing

- Patent certifications affect timing of approval
  - Paragraph I or II certification: FDA can approve the application "immediately," *i.e.*, as soon as the agency completes its scientific review
  - Paragraph III certification: FDA cannot approve the application until the patent expires
  - Paragraph IV certification: Applicant seeks approval before expiration of patent, but triggers a host of consequences for NDA holder, ANDA applicant and FDA
- If there are multiple patents, FDA will run through the analysis for each patent and certification

Paragraph IV Process

- ANDA applicant must provide notice to NDA holder and patent owner (if different), within 20 days of the ANDA being "received" by FDA
  - Earlier notice is invalid (21 CFR 314.52(b)(2))
- Paragraph IV Notice Letter must include "detailed statement of factual and legal basis of applicant's opinion that the patent is not valid, unenforceable, or will not be infringed"
  - Paragraph IV Notice Letter is not confidential
- If litigation is filed within 45 days of receipt of Notice Letter, a regulatory stay arises and prevents FDA from granting final approval to the ANDA
  - Typically referred to as "30-month stay" but operates a bit differently when NDA product has "NCE" exclusivity → 7.5 years from date of NDA approval

Section viii Statement

- A statement that the applicant does not seek approval for a method of use claimed by the patent and approved in the NDA
  - An alternative to a patent certification
  - No notice required, and no opportunity for H-W litigation and 30-month stay
- As a practical matter, this means that the ANDA applicant does not seek approval for an indication or condition of use described in the Use Code
  - The ANDA will have a labeling "carve out," a/k/a "skinny labeling"
    - For example, the ANDA could be approved for Indication 1 of the RLD but not the patent-protected Indication 2
- Only applies to patents with method of use claims
  - "Split certification" possible if patent has, *e.g.*, DS and MOU claims

LISTING PATENTS IN THE *ORANGE BOOK*

FILLING OUT FORMS 3542A AND 3542

Filling out Form FDA 3542

- Make sure you have the current version of the form; search here
- Background Information
  - NDA number: generally don't add supplement number
  - Drug description: follow Orange Book or Drugs@FDA for dosage forms and routes of administration
    - For 3542a, and prior to approval, labeling will generally be the guide
    - List entire active ingredient for salt forms
  - Strength:
    - List all if patent claims all strengths; if not, may need to list only subset of strengths
    - If already in Orange Book, list product number, e.g., ""Product 001] 200 mg

Filling out Form FDA 3542

- Background Information (continued)
  - Approval Date of NDA or Supplement
    - Can be tricky; generally go with NDA unless patent is listed for first time following sNDA approval; no clear instructions from FDA
  - Section 1: General
    - Fairly straightforward
    - Recommend including an e-mail address, but make sure it is monitored
    - Tells ANDA applicant where to send Paragraph IV Notice Letter
  - Section 1.e US agent
    - If the patent owner and/or NDA holder is a foreign entity, there needs to be a US agent
    - Identify name and entity or entities for whom they are US agent

Filling out Form FDA 3542

- Section 1: General (continued)
  - Questions 1.g and 1.h:
    - Only select YES in 1.g if patent has been submitted on a 3542, as when the patent is being resubmitted as part of a supplement
    - Previous submission in a 3542a does ***not*** trigger a YES here
  - Question 1.h: Identify the changes thoroughly and describe what action the change is related to (1) FDA action, e.g., sNDA approval; (2) action on the patent, *e.g.*, PTE, litigation or PTO action
    - FDA is trying to determine if the patent information is "untimely"
    - FDA can be nitpicky here: "Remove Use Code U-XXXX and replace with new Use Code" rather than "change the Use Code"

Filling out Form FDA 3542

- Section 2: Drug Substance (Active Ingredient)
  - The dynamic form will guide you depending on your answers
    - Almost always: 2.1: No, 2.2: No, Rest: BLANK; or 2.1: YES, skip to 2.5: No, 2.6: NO, 2.7 N/A
  - 2.2 and 2.3 only if patent claims only a different polymorph
  - 2.7 "not applicable"; rarely encountered "product-by-process" patent
- Section 3, Drug Product (Composition/Formulation)
  - If no DP claims: NO, NO, N/A
  - If DP claims: YES, NO, N/A
  - NOTE: if either one of Section 2 (DS) or Section 3 (DP) is filled out with a "Yes," the other section can be left blank
  - Either will trigger a Paragraph IV certification

Filling out Form FDA 3542

- Section 4: Method of Use
  - 4.1 If no MOU claims, NO; and that's it for that section
  - 4.1 Single or multiple
    - Generally, only add multiple sections/Use Codes where there are multiple indications
    - See button to "Add Section 4.2"
    - Checking "No" in 4.1 will reset this section and allow you to start over, if needed
  - 4.2 Patent claim numbers: list them out (1, 2, 3) or range (1-3)
    - "Reasonable to assert" is broad standard, particularly prior to, *e.g.,* claim construction
    - Better to list claims than not; risk of not being able to assert later
    - If multiple claims are clearly listable, risk of adding a "questionable" claim would appear to be low
  - 4.2 always answer YES to question on the right if you've answered YES in 4.1

Filling out Form FDA 3542

- Question 4.2a: Labeling sections
  - Follow FDA's format:
    - Section 1, subsection N/A
    - Section 2, subsections 1, 2, 3
  - Be broader rather than narrower; risk of not being able to assert later
  - Sections 1, 2, 3, 11, 12 and 14 are almost always included
  - Others as applicable
  - Don't attach or highlight labeling

Filling out Form FDA 3542

- Question 4.2b: Use Code (250 characters)
  - Can only cover the ***approved use as described in the labeling***
  - The overlap of the patent claims and the approved use described in the labeling
    - Biggest change in 2016 Final Rule
- The Use Code determines whether FDA can approve an ANDA with a labeling carve out/skinny labeling
  - This is why FDA perceives "overbroad" Use Codes as harmful
  - Easy example is a patent covering only one of two approved indications: can't simply list both indications in Use Code
- FDA says that ANDA's labeling cannot disclose the approved use, as described in the Use Code, but that agency has authority to interpret which parts of the labeling describe the Use Code

Filling out Form FDA 3542

- Section 5 No relevant patents
  - Never used this before; maybe for the rare NDA with no patents?
- Section 6
  - Signature of "authorized official" of NDA holder or patent owner
  - If signing electronically, fill out date first
  - 6.3 US agent signature needed only if person signing in 6.2 is not in US
- NDA Holder/Patent Owner/Authorized Official
  - No real preference between NDA Holder or NDA Holder's Attorney….

Miscellaneous questions

- Can we change approaches between 3542a and 3542?
  - Yes, because FDA is generally only going to rely on 3542
- How is a patent delisted?
  - Delist request letter
  - After litigation, within 14 days of court order
  - Sometimes patent will stay in Orange Book with Delist Requested "flag," if the patent is relevant to ANDA 180-day exclusivity

LISTING PATENTS IN THE *ORANGE BOOK*

ENFORCEMENT AND OTHER CHALLENGES

Failure to Meet Patent Listing Obligations

- Failure to list a patent that qualifies
  - Submission of Form FDA 3542/3542a is required even if there are no patents; there is a specific box to check in that case
  - Forms 3542a and 3542 contain a certification, under penalty of perjury, that the form is "accurate and complete" and complies with 21 CFR 314.53, and a warning that a willful and knowing false statement is a criminal violation of 18 USC 1001
  - Failure to submit required patent information is grounds under statute for FDA to refuse to approve the application → HAS NEVER HAPPENED
    - As a practical matter, if a patent is not listed, the NDA holder loses the opportunity to initiate patent litigation and thereby benefit form the 30-month stay

Failure to Meet Patent Listing Obligations

- Listing a patent that does not qualify for listing
  - Certification on Form FDA 3542 and Form FDA 3542a
  - A finding by FDA that an NDA contains a material false statement of fact is grounds for withdrawing approval → HAS NEVER HAPPENED
  - As a practical matter, can create significant risk
    - Public patent dispute process or H-W litigation counterclaim
    - Antitrust/competition risk
  - REMS and device patents are big issue right now (see below)
- Improper Use Code
  - *Caraco* case: SCOTUS held that counterclaim can be used to address Use Codes
  - Precedex letter decision

Failure to Meet Patent Listing Obligations

- Failure to timely list a patent
  - Reminder: Patent issued while application is pending or after approval must be listed within 30 days of approval (a so-called "later-issued patent")
  - If a later-issued patent is "timely filed," a pending ANDA must certify to the patent
    - Litigation can be initiated, but there is no 30-month stay for a Paragraph IV to a patent listed ***after submission of the ANDA***
  - If the patent is "untimely filed," meaning the 30-day deadline has been missed, a ***pending ANDA*** is generally not required to certify → no 30-month stay
    - ANDA submitted after listing of "untimely filed" patent must certify, and a Paragraph IV can be basis for H-W litigation and 30-month stay
  - Theoretically grounds for FDA to withdraw approval of the NDA → HAS NEVER HAPPENED

Patent Listing Dispute: Administrative Process

- There are two avenues for third parties to challenge the accuracy of patent information listed in the Orange Book
  - Administrative "Patent Listing Dispute" procedure under 21 CFR 314.53(f)
    - Challenger sends written notice to FDA with specific grounds
    - If dispute related to Use Code, 250-word narrative
    - FDA sends anonymized letter to NDA holder
    - NDA holder must respond within 30 days
      - If related to Use Code, 250-word narrative and verification (identical to that on forms)
  - FDA will do what NDA holder says; ministerial role
    - ANDA applicant has to go along with what NDA holder submits
  - Information about the dispute is posted on FDA website

FDA's Patent Listing Disputes List

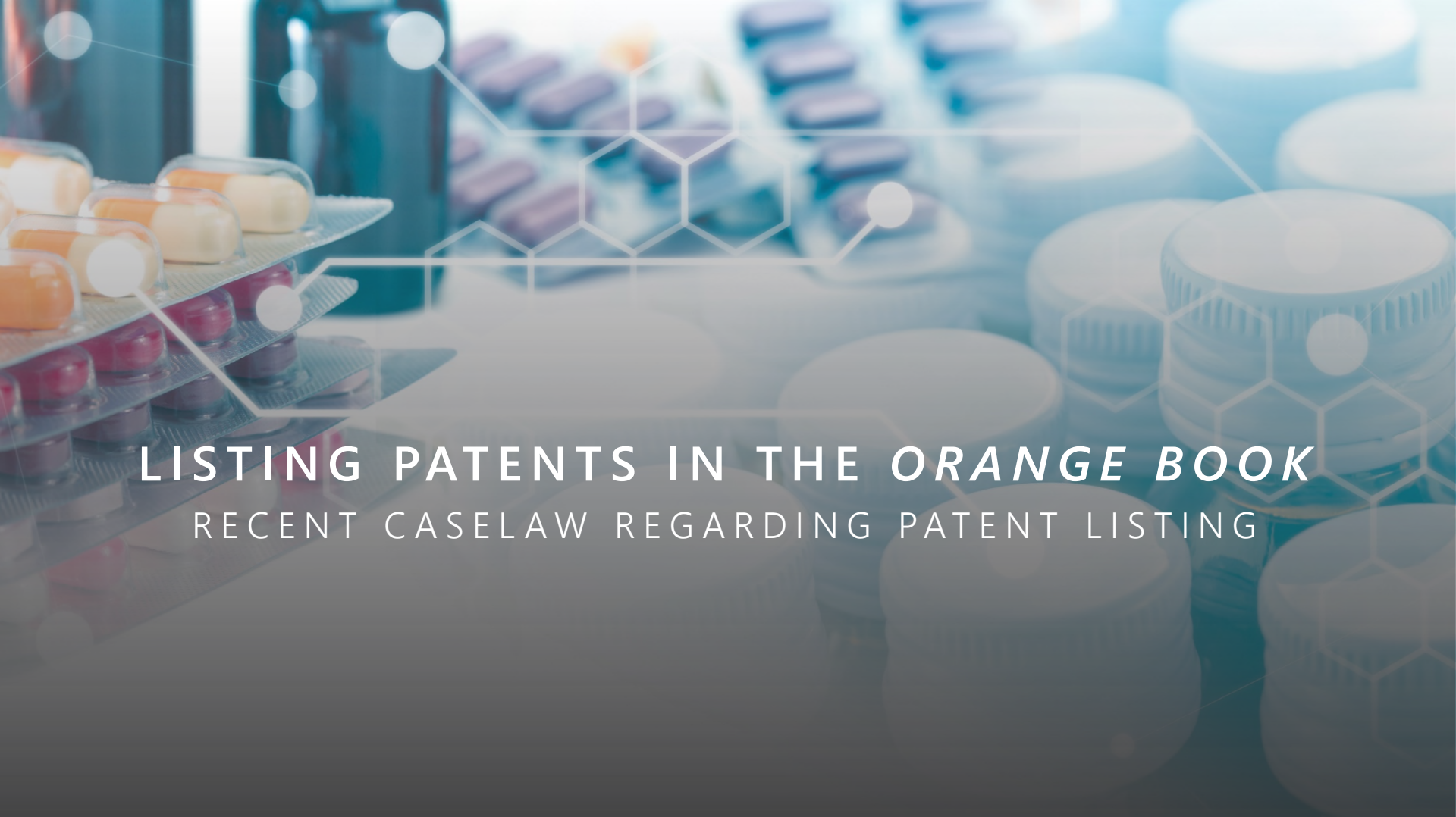
Patent Listing Disputes

Current through June 9, 2023

Established Drug Product Name	NDA Number	NDA Holder	Strength(s)	Relevant U.S. Patent Number(s)	Type of Patent Claim	Original Use Code (if applicable)	Revised Use Code (if applicable)	Due Date for NDA Holder Response	NDA Holder Response Date	Dispute Outcome
propofol	019627	Fresenius Kabi USA LLC	10mg/ml	8476010	Disputes Not Related to Use Code	N/A	N/A	4/21/2023	4/21/2023	No Orange Book Changes
phentolamine mesylate	022159	Septodont Holding	0.4mg/1.7ml	7229630, 7575757	Disputes Not Related to Use Code	N/A	N/A	1/21/2023	1/13/2023	Patent Listing Updated
epinephrine	205029	BPI Labs LLC	1mg/mL	9283197	Disputes Not Related to Use Code	N/A	N/A	12/9/2022	12/1/2022	No Orange Book Changes
amifampridine phosphate	208078	Catalyst Pharmaceuticals Inc	10mg	10636088	Disputes Not Related to Use Code	N/A	N/A	11/16/2022	11/8/2022	No Orange Book Changes
pitolisant hydrochloride	211150	Harmony Biosciences LLC	4.45mg 17.8mg	8486947	Method of Use	U-1102: Method of treating cataplexy in patients with narcolepsy	N/A	8/7/2022	8/4/2022	No Orange Book Changes
ganaxolone	215904	Marinus Pharmaceuticals Inc	50 mg/mL	8022054	Disputes Not Related to Use Code	N/A	N/A	7/30/2022	7/19/2022	Patent Listing Updated
baricitinib	207924	Eli Lilly Co	1mg 2mg 4mg	9089574, 11045474	Disputes Not Related to Use Code	N/A	N/A	6/7/2022	6/24/2022	No Orange Book Changes
tipiracil hydrochloride; trifluridine	207981	Taiho Oncology Inc	6.14mg; 15mg 8.19mg; 20mg	10960004	Method of Use	U-2642: Method of treating cancer by detecting a creatinine clearance of a patient and administering Lonsurf	N/A	5/28/2022	5/24/2022	No Orange Book Changes
tipiracil hydrochloride; trifluridine	207981	Taiho Oncology Inc	6.14mg; 15mg 8.19mg; 20mg	10456399	Method of Use	U-2642: Method of treating cancer by detecting a creatinine clearance of a patient and administering Lonsurf	N/A	5/26/2022	5/24/2022	No Orange Book Changes
fostamatinib disodium	209299	Rigel Pharmaceuticals Inc	100 mg 150 mg	8263122, 8652492	Disputes Not Related to Use Code	N/A	N/A	4/8/2022	4/5/2022	No Orange Book Changes
famotidine; ibuprofen	022519	Horizon Medicines LLC	26.6mg; 800mg	8067033	Disputes Not Related to Use Code	N/A	N/A	3/12/2022	2/22/2022	Patent Listing Updated

Patent Listing Dispute: Litigation Counterclaim

- In Hatch-Waxman patent litigation, an ANDA applicant can assert a counterclaim regarding accuracy of patent listing information
  - ANDA applicant can seek order requiring NDA holder to correct or delete patent information
- In 2012 *Caraco* case, SCOTUS (J. Kagan) held that challenge to Use Code was permissible under this provisions
  - Justice Sotomayor noted that the timing of the counterclaim undermined the utility of this remedy



LISTING PATENTS IN THE *ORANGE BOOK*

RECENT CASELAW REGARDING PATENT LISTING

Special Topics:
REMS and Device Patents

- Historically uncertain whether device patents could be listed
  - A patent that claims use of the drug with a specific device
  - A patent that claims only the device
  - A patent that claims a component of the device
- Multiple sponsors sought advisory opinions between 2005 and 2011, but FDA declined to opine on whether device patents could be listed, and under what circumstances
- So, sponsors have typically listed device patents, based on regulatory language and preambles
  - Devices can be "integral" parts of the finished dosage form, and dosage forms are identified in the OB
  - "The key factor is whether the patent being submitted claims the finished dosage form of the approved drug product." 68 FR 36675, 36680 (June 18, 2003)

Special Topics:
REMS and Device Patents

- In 2020, FDA opened a docket seeking stakeholder input on these issues, Docket No. FDA-2020-N-1127
  - Drug product/device patents
  - REMS patents
  - Digital applications associated with drug products
- Recent exchanges between FDA and USPTO
  - FDA working group

Listing Device Patents in the Orange Book – *In Re: Lantus*

- *In Re: Lantus Direct Purchaser Antitrust Litigation,* 950 F.3d 1 (1st Cir. 2020)
- Sanofi-Aventis listed a patent (the '864 Patent) with its NDA for Lantus SoloSTAR (insulin glargine), a disposable injector pen product
  - US Patent No. 8,556,864 is entitled "Drive mechanisms suitable for use in drug delivery devices" and generally claims a component of the SoloSTAR pen used with the dosage selector
  - Ten claims concerning aspects of a "drive mechanism" that serves as a part of a pen injector
  - Does not expressly identify insulin glargine in claims
- Plaintiffs brought antitrust suit, alleging that patent was improperly listed, which led to H-W litigation and a 30-month stay, ultimately delaying competition and resulting in higher prices for plaintiffs

Listing Device Patents in the Orange Book – *In Re: Lantus*

- Massachusetts District Court granted Sanofi's motion to dismiss, on the basis that FDA's patent listing requirements were ambiguous as to listing of device patents that do not claim a drug substance/active ingredient; thus, Sanofi's patent listing was reasonable
- On appeal, however, the First Circuit overruled the district court
  - The appellate court concluded that "[t]he statute and regulations clearly require that only patents that claim the drug for which the NDA is submitted should be listed in the Orange Book[, and] [t]he '864 patent, which neither claims nor even mentions insulin glargine or the Lantus SoloSTAR, does not fit the bill."
  - Remanded, and litigation is ongoing

Listing REMS Patents in the Orange Book – *Jazz v. Avadel CNS*

- This dispute relates to Jazz Pharma's Xyrem (sodium oxybate), a drug used to treat narcolepsy
  - Xyrem was approved with a Risk Evaluation and Mitigation Strategy (REMS) to address safety risks and concerns about abuse/misuse of the drug, whose active ingredient is a salt of GHB; among other things, the REMS employs a central pharmacy and computer database to track prescriptions, patients, and prescribers
- Jazz obtained a patent on a "computer implemented system" that keeps track of ***prescription drugs used to treat a narcoleptic patient*** that are at risk for misuse, abuse or diversion
  - That patent was listed in the Orange Book as a "method of use" patent
  - U-1110: METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION
  - The patent does not expressly claim the active ingredient or drug substance of Xyrem
- Seeking to launch its own sodium oxybate product, Avadel initially submitted a "(B)(2)(b) statement" (the equivalent of a "section viii statement" for a 505(b)(2) NDA)
  - FDA refused to approve the labeling carve out proposed by Avadel and required Avadel to submit a Paragraph IV certification to the REMS patent, *Avadel v. Becerra* (DDC 2022)

Listing REMS Patents in the Orange Book – *Jazz v. Avadel CNS*

- Following the Paragraph IV certification, Jazz sued Avadel for infringement in the District Court of Delaware, and Avadel counterclaimed for delisting the REMS patent from the Orange Book
  - Litigation resulted in 30-month stay on FDA approval
  - FTC filed an amicus brief asserting that the patent was improperly listed
- March 2023: The Federal Circuit recently affirmed the District Court decision in favor of Avadel
  - The District Court held, and the Federal Court affirmed, that the REMS patent should be de-listed, because it did not claim an approved method of using the drug
  - "On its face, the delisting statute does not require inquiring as to whether the NDA holder was authorized to list the patent in the first instance."
  - "In evaluating the counterclaim, the district court found that, as a matter of claim construction, the '963 patent claims a system and thus does not claim an approved method of use. The district court subsequently ordered Jazz to ask the FDA to delist the '963 patent."

Listing REMS Patents in the Orange Book – *Jazz v. Avadel CNS*

- In reaching its conclusion, the Federal Circuit affirmed the District Court's construction of the REMS patent's claims as "system," not "method," claims
  - Jazz was ordered to de-list the REMS patent; request for de-listing was submitted on March 1
  - No holding that a REMS patent is *per se* ineligible for listing
- Following patent delist request on approximately March 1, 2023, FDA approved Avadel's Lumryz (sodium oxybate) on May 1, 2023
  - Orphan drug issues also needed resolution, prior to approval of Lumryz

Orange Book Patent Listing Eligibility

FDA takes a "ministerial" approach to patent issues, including listing and description of Use Codes

- FDA has long deferred taking a position on whether certain patents covering REMS or device components are eligible for listing in the Orange Book
- FDA maintains authority to determine whether a labeling carve out is permissible, because it does not disclose the patented use, ***as described in the Use Code***

In the absence of clear guidance from FDA, the federal courts have stepped in, in the context of Hatch-Waxman patent litigation and antitrust litigation

- REMS patents: *Jazz v. Avadel CNS* (Fed. Cir. 2023)
- Device patents: *In re: Lantus Direct Purchaser Antitrust Litigation* (950 F.3d 1 (1st Cir. 2020))

Best Practices for Orange Book Patent Listings

- Until FDA takes steps to clarify listing requirements for certain REMS and medical device patents, heightened scrutiny is required when evaluating the eligibility of such patents for listing in the Orange Book, including the validity of existing listings
  - Involvement of antitrust, IP and regulatory counsel in listing decisions is advisable
  - NDA holders should ensure that their regulatory and IP strategies are well-aligned
- Issues are likely to arise particularly when such patents are the latest expiring or last ones left in the Orange Book

LISTING PATENTS IN THE *ORANGE BOOK*

SPECIAL TOPICS

Special Topics: Pediatric Exclusivity

- Under the Best Pharmaceuticals for Children Act (BPCA), if an NDA holder completes (and submits the results to FDA) pediatric studies described in a Written Request, FDA grants pediatric exclusivity
- If pediatric exclusivity is granted, FDA adds a 6-month extension to patents and other regulatory exclusivities (3-year, 5-year NCE, 7-year orphan, or 12-year BLA) listed in the Orange Book on the day that the pediatric exclusivity is awarded
  - Exception: patents or exclusivities that will expire within 9 months
- For regulatory exclusivity, application is straightforward: the time period is extended by 6 months, *e.g.*, 7-year orphan exclusivity becomes 7.5 years
  - More complicated for 5-year NCE exclusivity, but effectively adds 6 months to exclusivity periods and associated litigation stay
- FDA recently issued draft guidance to address these issues, with some potential changes

Pediatric Exclusivity: When does it attach to a patent?

- Pediatric exclusivity is not an extension of the term of the patent, like PTE or PTA; pediatric exclusivity is an extension of the preclusive effect of the patent on FDA's authority to approve an ANDA
- For patents, pediatric exclusivity is applied somewhat differently, and whether it attaches will depend on ANDA's patent certification(s) and the outcome of the litigation
  - Paragraph II or III certification: the 6-month extension automatically attaches, and FDA cannot approve the ANDA until 6 months after patent expiration
  - Paragraph IV certification: the 6-month extension only attaches if NDA holder prevails in patent litigation, *i.e.*, obtains a favorable district court judgment that the patent is valid and infringed
    - If patent expires while litigation is pending, the 6-month extension will automatically attach, because the ANDA applicant's Paragraph IV is "deemed" to be a Paragraph III certification immediately upon expiration of the patent

Pediatric Exclusivity: Unusual applications

- As noted above, if pediatric exclusivity is granted, FDA adds a 6-month extension to patent and other exclusivities that are listed in the Orange Book on the day that the pediatric exclusivity is awarded, for all of the sponsor's approved or pending NDAs containing the same active moiety
  - Later-issued patents can also be extended, if they relate back to the product approved at the time of the pediatric exclusivity award
    - My test: Could the patent – if it had issued earlier – have been listed with the NDA at the time of the pediatric exclusivity award
    - Not provided for in new guidance
  - A patent that becomes listable because it covers a new indication approved after the award of pediatric exclusivity → no 6-month extension
  - Later-approved products can also have some patents extended
    - Generally, patents extended when listed with previously approved NDAs

Pediatric Exclusivity: Fixed-dose combination products

- NOT addressed in new draft guidance
- Pediatric exclusivity based on studies of a product with a single active ingredient
  - Applies to all NDAs containing same active moiety, even fixed-dose combination products
  - For example, pediatric exclusivity awarded for studies on Ziagen (abacavir) was applied to the patents listed with Ziagen at the time of the award, and whenever those patents were listed with later-approved products containing abacavir, *e.g.*, Epzicom (abacavir sulfate; lamivudine)
- Pediatric exclusivity based on studies of a fixed-dose combination product
  - Historically, would extend patents and regulatory exclusivities in other approved NDAs containing any of the same active moieties
  - FDA may be reluctant to issue a Written Request in these circumstances

Special Topics: Patent Provisions for BLAs

- The BPCIA divorced biosimilar approval from patent litigation process
  - The statute does include detailed "patent dance" provisions, in which the BLA holder and the biosimilar applicant must exchange lists of patents to be litigated according to precise deadlines
  - FDA generally stays out of it
- As a result, there is no global patent listing requirement for BLAs as there is for NDAs
- Limited exception: when the BLA holder provides its list of patents to the biosimilar applicant, the BLA holder must also notify FDA within 30 days, including a list of patents and expiration dates
  - FDA will publish this list alongside the Purple Book
  - Enacted in 2021

Resources

- Form FDA 3542 and Instructions
- Form FDA 3542a and instructions
- 21 USC 355(b) (patent listing statute)
- 21 CFR 314.53 (patent listing regulation)
- 21 CFR 314.50(i); 314.94(a)(12) (patent certification regulation)
- 2016 Rulemaking
  - Final Rule, 81 FR 69580 (Oct. 6, 2016)
  - Proposed Rule, 80 FR 6802 (Feb. 6, 2015)
- 42 USC 262 (BLAs only)

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