



Risk Management or Risky Patents – a look at the FDA's REMS program and REMS patents

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Erik Huestis
Jeffrey I. D. Lewis
Tina Papagiannopoulos
Matthew Piscitelli

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Today's Panelists



Jeffrey I.D. Lewis

Partner - Registered Patent Attorney
New York
212.812.0304
jidlewis@foleyhoag.com

A chemical engineer and registered patent attorney, Jeff concentrates on patent and trademark litigation, counseling and licensing, as well as other intellectual property and general litigation including trademark and trade secret matters.



Tina Papagiannopoulos

Counsel
Washington, DC
202.261.7344
tpapagiannopoulos@foleyhoag.com

Assists clients with a variety of regulatory, policy, and compliance matters related to the U.S. Food & Drug Administration (FDA) and the Federal Trade Commission (FTC), with a primary focus on therapeutics.



Erik Huestis

Partner - Registered Patent Attorney
New York
212.812.0325
ehuestis@foleyhoag.com

Counsels technology companies and research universities in patent matters in computer science, including artificial intelligence in the genomics and medical imaging space, cryptography, quantum computing, and neuromorphic computing.



Matthew Piscitelli

Associate
Washington, DC
202.261.7462
mpiscitelli@foleyhoag.com

Provides comprehensive advice to FDA-regulated clients on topics including clinical trials, manufacturing compliance, product exclusivity, and advertising and promotion.

General Information

- A recording of today's presentation will be circulated following the event
- **CLE:**
 - A CLE Code will be provided later in the presentation
 - CLE credit is available to attendees of the live presentation only
- **QUESTIONS:**
 - Add your questions to the Q+A Section

The views expressed are solely those of the speakers in the context of this discussion. No views should be imputed to employers, clients or others.

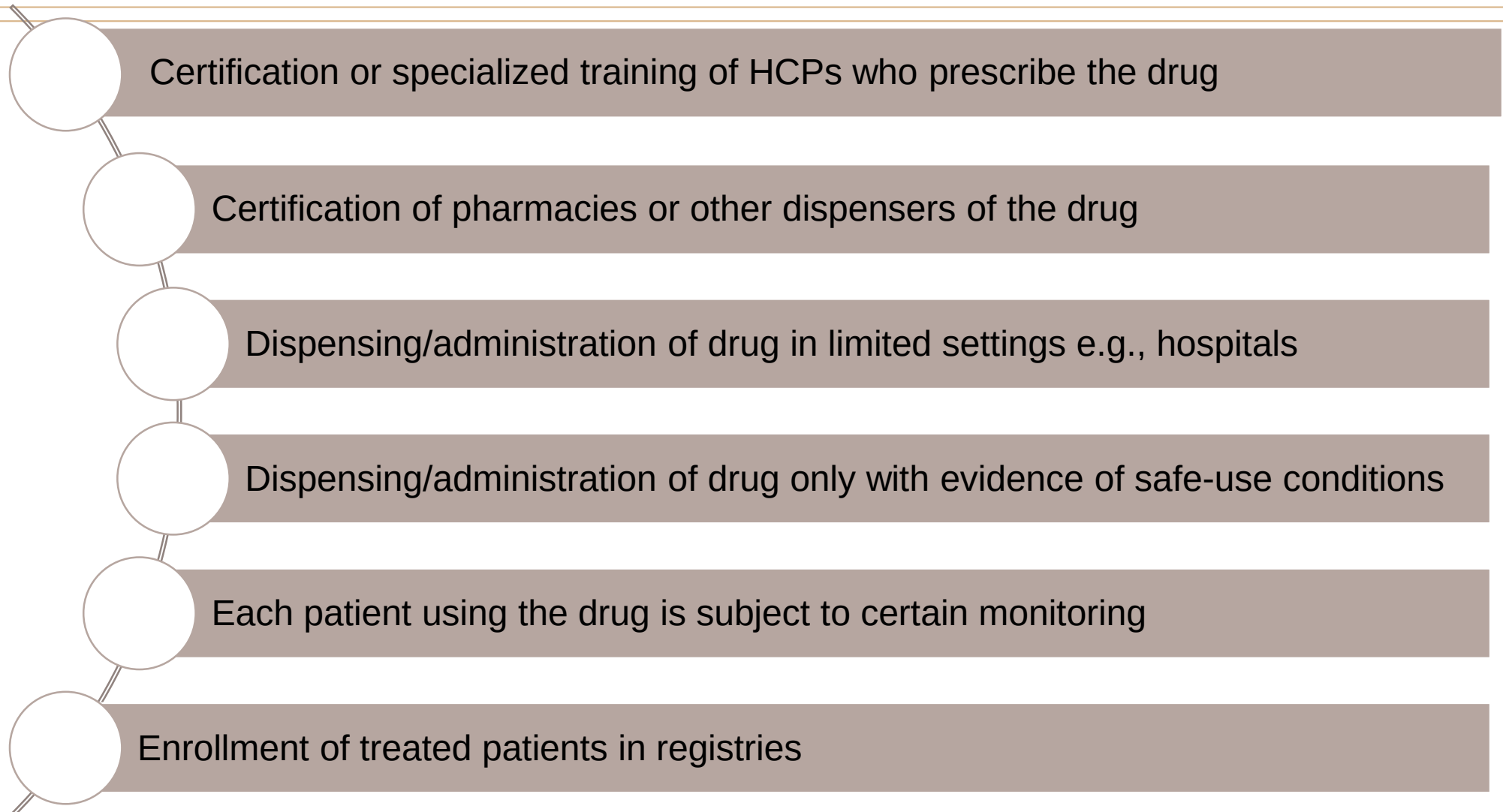


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Risk Evaluation and Mitigation Strategies (“REMS”)

- **Risk Evaluation and Mitigation Strategy (REMS)** is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks
 - Not designed to mitigate all the adverse events of a medication
 - REMS focus on preventing, monitoring and/or managing a specific serious risk
- REMS may take various forms including elements to assure safe use (**ETASU**)
- Other requirements may include patient medication guides, prescriber materials, and special methods for distribution and administration of drugs
- There are currently 67 active REMS programs

Elements to Assure Safe Use (ETASU)



REMS Examples

Ambrisentan Shared System REMS

- Ambrisentan products are indicated for treatment of pulmonary hypertension and potential side effects include teratogenic effects of fetuses
- Patients, prescribers, and pharmacies must enroll in the REMS program
- Female patients, especially those with the ability to get pregnant, must undergo specific counseling and pregnancy testing protocols

REMS Examples, Cont.

Opioid Analgesic Shared System REMS

- Instituted in 2018 as a means to combat the opioid addiction epidemic
- Opioid analgesic manufactures must prepare and disseminate risk information to DEA-registered prescribers and facilities
- Manufacturers must maintain an opioid analgesic risks website and the resources can be used by prescribers to fulfill continuing education requirements

“Serious Safety Concerns”

- The Federal Food, Drug, and Cosmetic Act (FDCA) outlines when a REMS is necessary and FDA uses the following six factors when determining the necessity of a REMS:
 - The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
 - The expected benefit of the drug with respect to the disease or condition;
 - The seriousness of the disease or condition that is to be treated with the drug;
 - Whether the drug is a new molecular entity;
 - The expected or actual duration of treatment with the drug; and
 - The estimated size of the population likely to use the drug.

REMS: FDA’s Application of Statutory Factors in Determining When a REMS Is Necessary

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2019
Drug Safety

REMS –versus– Adverse Event

- An adverse event is any undesirable experience associated with the use of a medicine in a patient
 - FDA requires manufacturers to (1) report serious adverse events and (2) respond to serious adverse events received in the FDA Adverse Event Reporting System (FAERS)
 - Serious adverse events are adverse events that lead to hospitalization, serious injury, disability, death, and other important medical events
- Products with a REMS may have additional reporting requirements
 - Through REMS-required labeling and warnings, FDA and manufacturers hope to reduce instances of adverse events associated with specific risks

Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
MEDWATCH
FORM 3500A
For use by user-facilities, importers, distributors, and manufacturers for MANDATORY reporting

Form Approved: OMB No. 0910-0291
Expires: 6-30-2025
See PRA statement on page 6.

FDA USE ONLY

Mr report #
UF/Importer Report #
Exemption/Variance #

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-JAN-1900.

A. PATIENT INFORMATION

1. Patient Identifier (in confidence)

2. Age
☐ Year(s) ☐ Week(s) or Date of Birth (e.g., 01-Jan-1900)
☐ Month(s) ☐ Day(s)

3a. Sex: Enter the patient's sex at birth (the sex that a person has or was assigned to at birth).
☐ Male ☐ Undifferentiated ☐ Female ☐ Decline to answer

3b. Gender: Enter the patient's current gender (how the patient thinks of themself).
☐ Cisgender man/boy (gender corresponds with birth sex) ☐ Transgender woman/trans woman/ male-to-female (MTF)
☐ Cisgender woman/girl (gender corresponds with birth sex) ☐ Other gender category; please specify:
☐ Transgender man/trans man/ female-to-male (FTM) ☐ Decline to answer

4. Weight
☐ lb ☐ kg

5. Ethnicity (Check one)
☐ Hispanic/Latino ☐ Not Hispanic/Latino

6. Race (check all that apply)
☐ American Indian/Alaska Native ☐ Native Hawaiian/ Other Pacific Islander
☐ Asian ☐ Black or African American ☐ White

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Type of Report (check all that apply)
☐ Adverse Event
☐ Product Problem (e.g., defects/malfunctions)

2. Outcome Attributed to Adverse Event (check all that apply)
☐ Death - Date of death (01-JAN-1900):
☐ Life-threatening ☐ Required Intervention to Prevent Permanent Impairment/Damage
☐ Hospitalization (initial or prolonged) ☐ Disability or Permanent Damage
☐ Other Serious or Important Medical Events ☐ Congenital Anomaly/Birth Defects

3. Date of Event (01-JAN-1900)

4. Date of this Report (01-JAN-1900)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.
* Please see instructions.

Form FDA-3500A MedWatch(11/22) Page 1 of 7
(PREVIOUS EDITION OBSOLETE)

(continued on next page)

Patent-Independent REMS Market Access Issues

- Generic manufacturers need samples of brand products in order to conduct necessary equivalence tests
 - Brand manufacturers sometimes used strict REMS distribution requirements as a method to avoid providing samples to generic manufacturers for bioequivalence testing
 - The CREATES Act established a private right of action that allows developers to sue brand companies that refuse to sell them product samples needed to support their applications
- Generic manufacturers of a branded REMS product must also establish REMs
 - This is typically done as a “Shared-System” REMS, but generic applicants can now seek waivers to establish their own REMS programs
 - The waiver process was created to address concerns that generic applicants were foreclosed from participating in shared-system REMS established by brand companies.



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Patent Eligibility

- Claims cannot be directed solely to “abstract ideas, laws of nature and natural phenomena”
 - These “are the basic tools of scientific and technological work,” and so are not patentable as a matter of policy
- A “mere recitation of a judicial exception does not mean that the claim is ‘directed to’ that judicial exception.”
 - “a claim that recites a judicial exception is not directed to that judicial exception, if the claim as a whole ‘integrates the recited judicial exception into a practical application of that exception.’”
 - Conversely, “a claim reciting a judicial exception is now eligible... unless that exception is not integrated into a practical application of the exception.”

Current Guidance

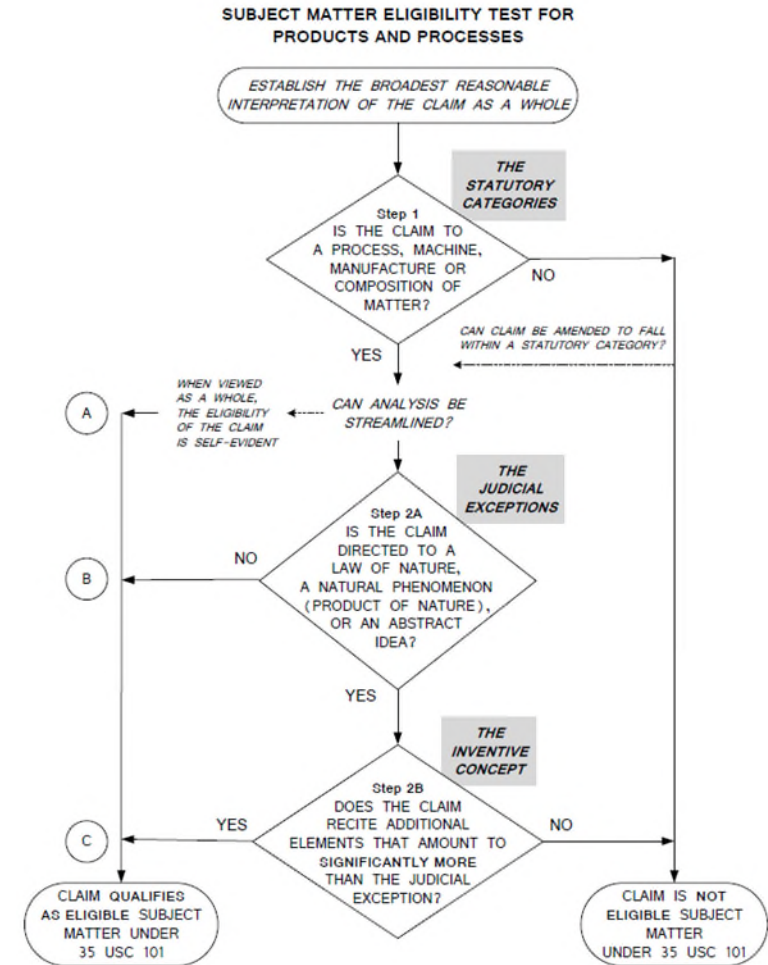
■ Abstract ideas include (January 2019 Guidance)

- “mathematical concepts”
 - ◆ can be as simple as a ratio between length and width, whether in an equation or in plain English
 - ◆ Includes any “mathematical calculations,” whether explicit or implicit
- “certain methods of organizing human activities”
 - ◆ generally limited to economic principles, commercial or legal interactions, personal behavior
- “mental processes”
 - ◆ includes methods that are performed with a computer, as long as a portion of the methods could be performed in the human mind
 - ◆ excludes methods that cannot **practically** be performed in the human mind
 - ◆ but in many cases, sweeps in processes that would be time and complexity prohibitive

Current Guidance

A claim may be patentable where it “integrates [the] judicial exception into a practical application [that] will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception.”

- improvement in the functioning of a computer, or an improvement to another technology or technical field
- but “generic computer components [] amount[] to mere instructions to implement the abstract idea on a computer”



How to Frame an Invention

- You don't patent a result
 - You patent a process, a machine, or a composition giving rise to a result
 - The benefits are important, but the invention relates to the features that give rise to the benefits

- Is this a technical solution to a technical problem?
 - What is the practical application?

- Consider narrower, varied coverage

“...but with...”

- Drill down below “but with”
 - But with the internet
 - But with blockchain
 - But with a neural network

- Is this a straightforward implementation of well-known theory on third party hardware?

- Increased importance of Broadest Reasonable Interpretation (BRI).

Specification Support

- Improvements in efficiency, runtime, and storage or memory bandwidth provide strong arguments, particularly when dealing with large datasets
- Is this a technical solution to a technical problem?
- Drill down below “but with”
- Express a concrete improvement to underlying computer technology
- Consider whether to lead with ASIC or integrated embodiments

Categories of Software Inventions

■ Algorithms

- Encryption
- Compression
- Routing
- Image Recognition
- Text Processing
- Intrusion Detection
- Feature Extraction

■ Software Architecture

- Message Flows
- Interactions of Software Components
- Distributed Storage and Processing

■ System Architecture

- Relationships Between Nodes in a Network
- Roles of Nodes in a System
- Big Data Systems
- Data Mining Techniques

■ Software for Enabling Hardware

- Storage Controllers
- Media Players
- Routers

■ User Interface Design

■ Neural Network Configurations

Avoid Abstraction

Abstract

- “We use a neural network to predict phenotype from sequencing data.”
- “Instead of sorting the data by hand, we use a classifier.”

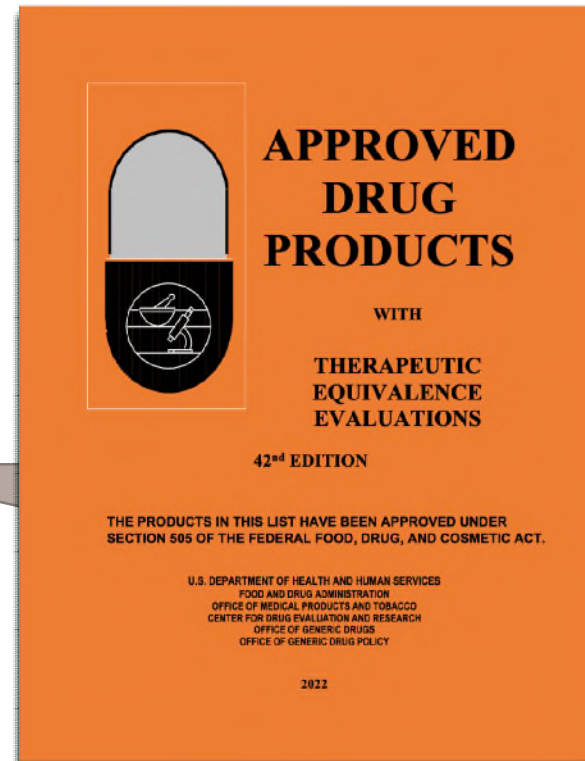
Specific

- “To predict phenotype, our system uses a pair of neural networks. The first is a convolutional neural network with a fully convolutional layer, which is trained to predict relevance of SNPs to a given phenotype of interest. The second is feed-forward network trained on the most relevant SNPs to predict phenotype.
- “We have designed an ensemble model using cascading SVMs for hierarchical classification.”

The Orange Book

Includes:

- **FDA-approved drug products**
 - Proprietary name
 - Generic name
 - Dosage
- **Related patent information**
 - Patent numbers
 - Patent expirations
 - NOT all relevant patents
- **Exclusivity information**



Listable:

- Composition of Matter, e.g.:
 - API
 - Ingredients
 - Formulation
- Method of Treatment / Administration (Use Codes)

Not listable:

- Synthetic methods
- Intermediates
- * Packaging
- * Metabolites

**FDA does not *substantively* review listed patent information;
FDA's role is "purely ministerial".**

aaiPharma Inc. v. Thompson, 296 F.3d 227 (4th Cir. 2002);
Apotex v. Thompson, 247 F.3d 1335, 1347 (Fed. Cir. 2003)

The Orange Book: **advantages** of listing



NDA – *required* to list certain types of patents.

21 U.S.C. § 355(b)(1) & (c)(2) [FD&C Act § 505(b)(1) & (c)(2); see 21 CFR 314.53(b)(1)]

An ANDA or 505(b)(2) applicant must provide a patent statement.

P-I = No patents listed P-II = Patents expired P-III = Wait for expiration P-IV = Invalid/Not infringed

Filing an ANDA with P-IV is an act of patent infringement.

35 USC § 271(e)(2)(A).

Prompt suit: Automatic 30-month stay of FDA approval.

(≥ ~6.5 years after initial NDA approval of NCE)

The Orange Book: **disadvantages** of listing

- 1 Possible admissions of scope of patents (e.g., claim construction) and bio-similarities
- 2 Listing can be subject to challenge: FDA or Courts
- 3 Declaration by submitter, signed under oath
- 4 Antitrust claims if not reasonably listed
- 5 Recent Federal Trade Commission activity

Jazz Pharms., Inc. v. Avadel CNS Pharms., LLC 60 F.4th 1373 (Fed. Cir. 2023)

- Narcolepsy Drug Xyrem® → “Date Rape Drug”
- NDA approval – REMS (prescribing / dispensing)
- '963 patent (2014 listed in *Orange Book*):
“Jazz's single-pharmacy distribution system, which **controls access** to abuse-prone prescription drugs prescribed to **narcolepsy patients** through a **central pharmacy** and computer database by **tracking prescriptions, patients, and prescribers.**” (60 F.4th at 1376)
- Avadel 2020 §505(b)(2) NDA: FT218 *with* REMS
 - FDA: Required certification on '963 patent
 - Jazz: Patent Suit *v. Avadel*
 - Avadel: Admin. Proc. Act. Suit *v. FDA*

Listable:

- Composition of Matter, *e.g.*:
 - API
 - Ingredients
 - Formulation
- Method of Treatment / Administration (Use Codes)

Not listable:

- * Synthetic methods/intermediates
- * Packaging
- * Metabolites

Jazz v. Avadel – Listing Challenge

- Challenging *Orange Book* Listings:

- FDA-based challenge
- Counterclaim to Hatch-Waxman patent suit

“... the applicant may assert a **counterclaim** seeking an order requiring the holder **to correct or delete the patent information** submitted by the holder ... on the ground that the patent does not claim either—

(aa) the **drug** for which the application was approved; or

(bb) an approved **method of using the drug.**” 21 U.S.C. §355(c)(3)(D)(ii)(I) (NDA); see §355(j)(5)(C)(ii)(I) (ANDA)

- Computer system **≠** Method of using the drug

- Dist. Ct.: Permanent Injunction to **delist '963 patent** from *Orange Book*

- Fed. Cir: Affirmed



Jazz v. Avadel – FTC Amicus Curiae

The strict statutory limits on Orange Book patent listings serve a vital purpose because **the listing process has significant implications for consumers and for competition.** ... [The] 30-month stay ... reflects Congress's intent to balance the interests of brand and generic drug manufacturers by facilitating the resolution of certain types of patent disputes before generic or 505(b)(2) products are introduced. **But when this stay is triggered by a patent that does not meet the statutory listing criteria, the stay merely blocks consumer access to a competing product that might reduce prices, improve quality, or both. Given the high cost of many drugs, even a short delay in competition can have enormous consequences for the public.**

Case 1:21-cv-00691-GBW Document 222-3 Filed 11/10/22 Page 1 of 27 PageID #: 4447

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC.,	
Plaintiff,	Civil Action No. 21-691-GBW
v.	
AVADEL CNS PHARMACEUTICALS, LLC,	
Defendant.	

FEDERAL TRADE COMMISSION'S BRIEF AS *AMICUS CURIAE*

HOLLY L. VEDOVA Director Bureau of Competition	MARKUS H. MEIER BRADLEY S. ALBERT DANIEL W. BUTRYMOWICZ REBEKAH S. CONLON REBECCA L. EGELAND ANUPAMA SAWKAR Attorneys for <i>Amicus Curiae</i> Federal Trade Commission 600 Pennsylvania Avenue, NW Washington, DC 20580 Tel: 202-326-3759
ANISHA DASGUPTA General Counsel Federal Trade Commission	



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FTC Policy – Sept. 14, 2023 Statement

- Supported by FDA
- “[P]harmaceutical companies ... could face **legal action** if they **improperly list patents** in the... ‘Orange Book’.”
- “Improperly listing patents in the Orange Book **may harm competition** from less expensive generic alternatives and keep prices artificially high, according to the policy statement. The **FTC will scrutinize improper Orange Book patent listings** as potential unfair methods of competition in violation of Section 5 of the FTC Act.”
- “... **illegitimately delay or lock out generic manufacturers** from entering the market, depriving Americans of access to lower-cost medicines and drug products ...”

www.ftc.gov/news-events/news/press-releases/2023/09/ftc-issues-policy-statement-brand-pharmaceutical-manufacturers-improper-listing-patents-food-drug

Statement of FTC Chair Khan

The FDA tentatively approved Avadel’s extended-release version ... but by that time, Jazz, another pharma company, had sued Avadel for **infringing Jazz’s “Risk Evaluation and Mitigation Strategies” (“REMS”) patent—a patent that had nothing to do with the drug itself or an approved method of using the drug.** Jazz cited the **Orange Book** to **automatically trigger the 30-month stay**, blocking Avadel from the market.



FTC Action – Nov. 7, 2023

FTC Challenges More Than 100 Patents as Improperly Listed in the FDA's Orange Book

Improper listings may delay lower-cost generic drug competition, stall drug development, and stifle innovation

“Today, the Federal Trade Commission (FTC) challenged more than **100 patents** held by manufacturers of brand-name asthma inhalers, epinephrine autoinjectors, and other drug products as **improperly or inaccurately listed in ... the ‘Orange Book.’**”

“The Commission has also **notified FDA that it disputes the accuracy or relevance of the listed information for these patents**, which may require that the manufacturers remove the listing or certify under penalty of perjury that the listings comply with applicable statutory and regulatory requirements.

“The **FTC sent notice letters to 10 companies**”

www.ftc.gov/news-events/news/press-releases/2023/11/ftc-challenges-more-100-patents-improperly-listed-fdas-orange-book; www.ftc.gov/legal-library/browse/warning-letters/81927

November 7, 2023 Notice Letter:

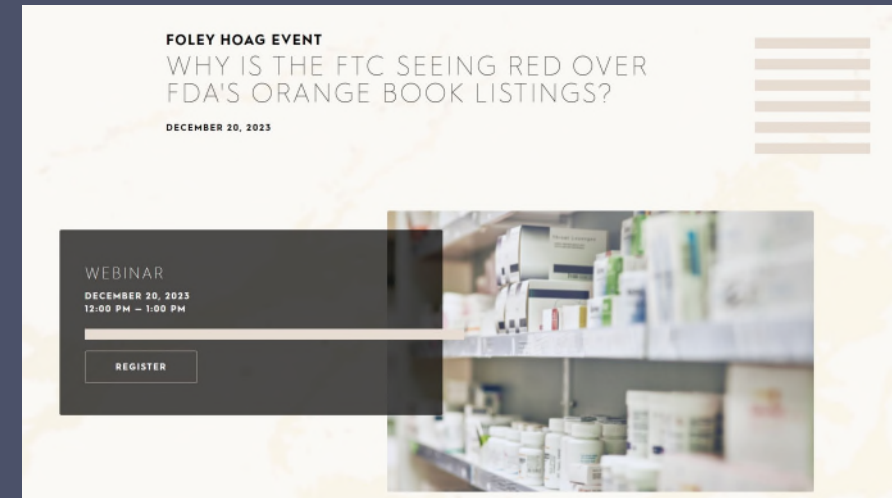
... certain patents have been improperly or inaccurately listed in the Orange Book ... We have opted to use the FDA's regulatory dispute process ... but we retain the right to take any further action the public interest may require, which may include investigating this conduct as an unfair method of competition under **Section 5 of the FTC Act**, 15 U.S.C. § 45, and as described in the **Policy Statement**.

Upcoming Webinar on Dec. 20th

On November 7, 2023, the FTC challenged over 100 patents that it says were improperly listed in the FDA's *Orange Book*, asserting that the listings could “drive up the prices Americans must pay for medicines and drug product while undermining fair and honest competition” (according to one Commissioner). These actions were not a surprise, however, because the FTC previewed them in its September *Policy Statement* specifically addressing the “Improper Listing of Patents in the *Orange Book*.” Specifically, our webinar will address:

- The standards for listing patents in the *Orange Book*;
- What it means for a patent to be listed in the *Orange Book* – and its real-world impact;
- FDA's mechanisms for dealing with patent listing challenges, both historically and today;
- FTC's September Policy Statement about *Orange Book* listings; and
- How the FTC looks at competition issues under Section 5 of the FTC Act, 15 U.S.C. § 45, and as described in its *Policy Statement*.

Register with the QR code below



Legislative Proposals

- Increasing Prescription Drug Competition Act (S. 574/H.R. 4692)
 - Sen. Maggie Hassan (D-N.H); Sen. Mike Braun (R-Ind); Rep. Elissa Slotkin (D-Mich)
- Enables FDA to immediately approve a generic drug if the only barrier to approval is a REMS patent
 - Certifications in generic drug applications with respect to patents that involve an ETASU for REMS requirements have no effect on the effective date of the drug's approval, notwithstanding any other provisions that allow for a stay of approval pending litigation outcomes (i.e., 30-month stay).
- Specifies that in a civil action alleging patent infringement with respect to REMS requirements, the sponsor of the approved brand-name drug may only seek damages from (rather than an injunction against) the generic drug applicant.



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