SCP 31 Sharing Session: Publicly Accessible Databases of Patent Status Information concerning Medicines and Vaccines

Overview of the Orange Book and the Off-Patent/Off-Exclusivity List

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Presentation Objectives

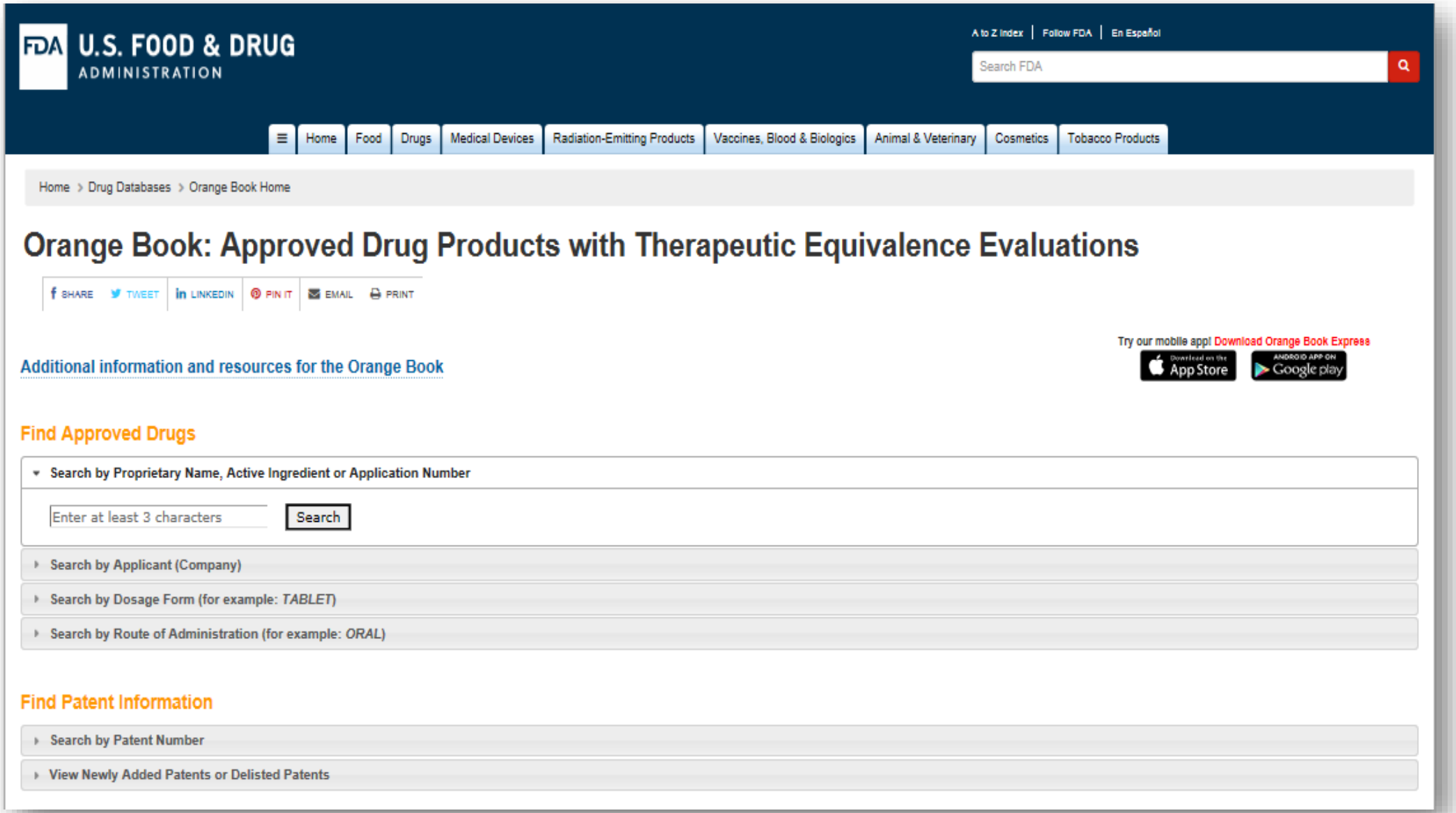
- Purpose and history of FDA's Orange Book – brief overview
- Key content and format of the OB's Drug Product Lists
- Patent information in the Orange Book & how to find it
  - Content and sources
  - What *isn't* in the Orange Book
- The Orange Book and generic drug applications
- The Off-Patent/Off-Exclusivity List

What is the Orange Book?

An FDA publication mandated under §505(j)(7)(A) of the Federal Food, Drug, & Cosmetic Act (FD&C Act).

- provides a listing of drugs approved as safe and effective
- serves as the regulatory resource for information on drug marketing availability, therapeutic equivalence, drug substitution, and patent and exclusivity data.
- is relied upon by applicants submitting a generic drug to the Agency to identify patent information required to be included in a generic drug application

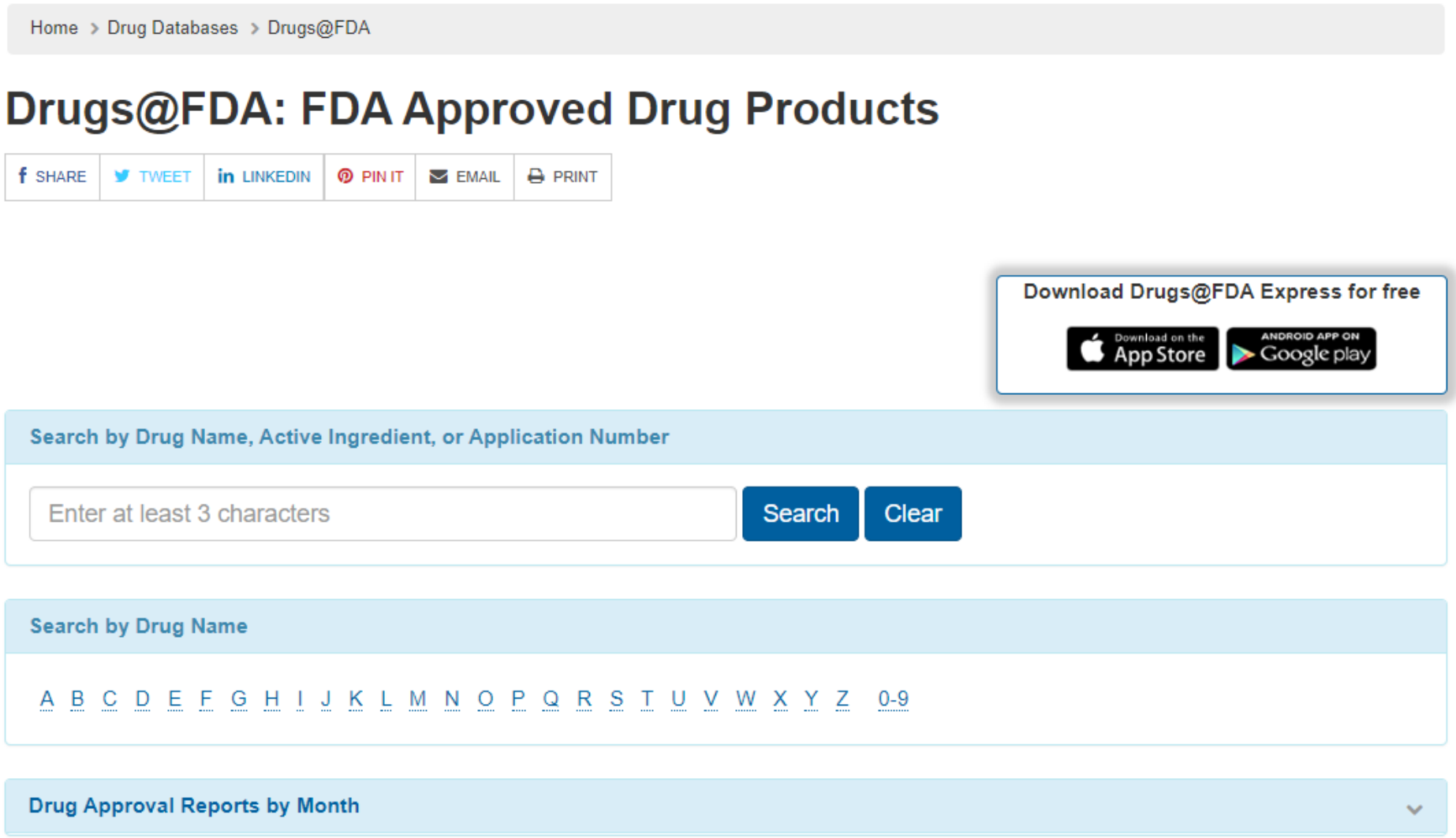
www.fda.gov/orangebook



Drug Product Listing Example - Online

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ORANGIUM HYDROCHLORIDE	RAINBOW	N12346	TABLET	ORAL	10MG	AB	RLD	RS	PHARMA CO INC
RX	ORANGIUM HYDROCHLORIDE	RAINBOW	N12346	TABLET	ORAL	20MG	AB	RLD		PHARMA CO INC
RX	ORANGIUM HYDROCHLORIDE	RAINBOW	N12346	TABLET	ORAL	40MG	AB	RLD		PHARMA CO INC
RX	ORANGIUM HYDROCHLORIDE	ORANGIUM HYDROCHLORIDE	A98765	TABLET	ORAL	10MG	AB			GENERIX LLC
RX	ORANGIUM HYDROCHLORIDE	ORANGIUM HYDROCHLORIDE	A98765	TABLET	ORAL	20MG	AB			GENERIX LLC
RX	ORANGIUM HYDROCHLORIDE	ORANGIUM HYDROCHLORIDE	A98765	TABLET	ORAL	40MG	AB			GENERIX LLC
Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder

Another Resource: Drugs@FDA



https://www.accessdata.fda.gov/scripts/cder/daf/

Orange Book: Patents and Exclusivities

- **Patents** protecting the approved drug substance, drug product, or approved methods of use

- Orange Book also identifies marketing **exclusivities** – statutorily provided periods of protection from competition, administered by FDA

Finding Patent and Exclusivity Information

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ORANGIUM HYDROCHLORIDE	RAINBOW	N12346	TABLET	ORAL	10MG	AB	RLD	RS	PHARMA CO INC
RX	ORANGIUM HYDROCHLORIDE	RAINBOW	N12346	TABLET	ORAL	20MG	AB	RLD		PHARMA CO INC
RX	ORANGIUM HYDROCHLORIDE	RAINBOW	N12346	TABLET	ORAL	40MG	AB	RLD		PHARMA CO INC
RX	ORANGIUM HYDROCHLORIDE	ORANGIUM HYDROCHLORIDE	A98765	TABLET	ORAL	10MG	AB			GENERIX LLC
RX	ORANGIUM HYDROCHLORIDE	ORANGIUM HYDROCHLORIDE	A98765	TABLET	ORAL	20MG	AB			GENERIX LLC
RX	ORANGIUM HYDROCHLORIDE	ORANGIUM HYDROCHLORIDE	A98765	TABLET	ORAL	40MG	AB			GENERIX LLC
Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder

Product Details for NDA 12346

Expand all

RAINBOW (ORANGIUM HYDROCHLORIDE)
10MG
Marketing Status: Prescription

Active Ingredient: ORANGIUM HYDROCHLORIDE
Proprietary Name: RAINBOW
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 10MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code: AB
Application Number: N12346
Product Number: 001
Approval Date: Jan 21, 2011
Applicant Holder Full Name: PHARMA CO INC
Marketing Status: Prescription
Patent and Exclusivity Information

RAINBOW (ORANGIUM HYDROCHLORIDE)
20MG
Marketing Status: Prescription

RAINBOW (ORANGIUM HYDROCHLORIDE)
40MG
Marketing Status: Prescription

- Separate listing for each strength
- Patents/Exclusivities may vary for different strengths

Patent and Exclusivity Information (online)

Patent and Exclusivity for: N308520

Product 001
LEMUR ACETATE (RINGTAIL) SOLUTION 300MG

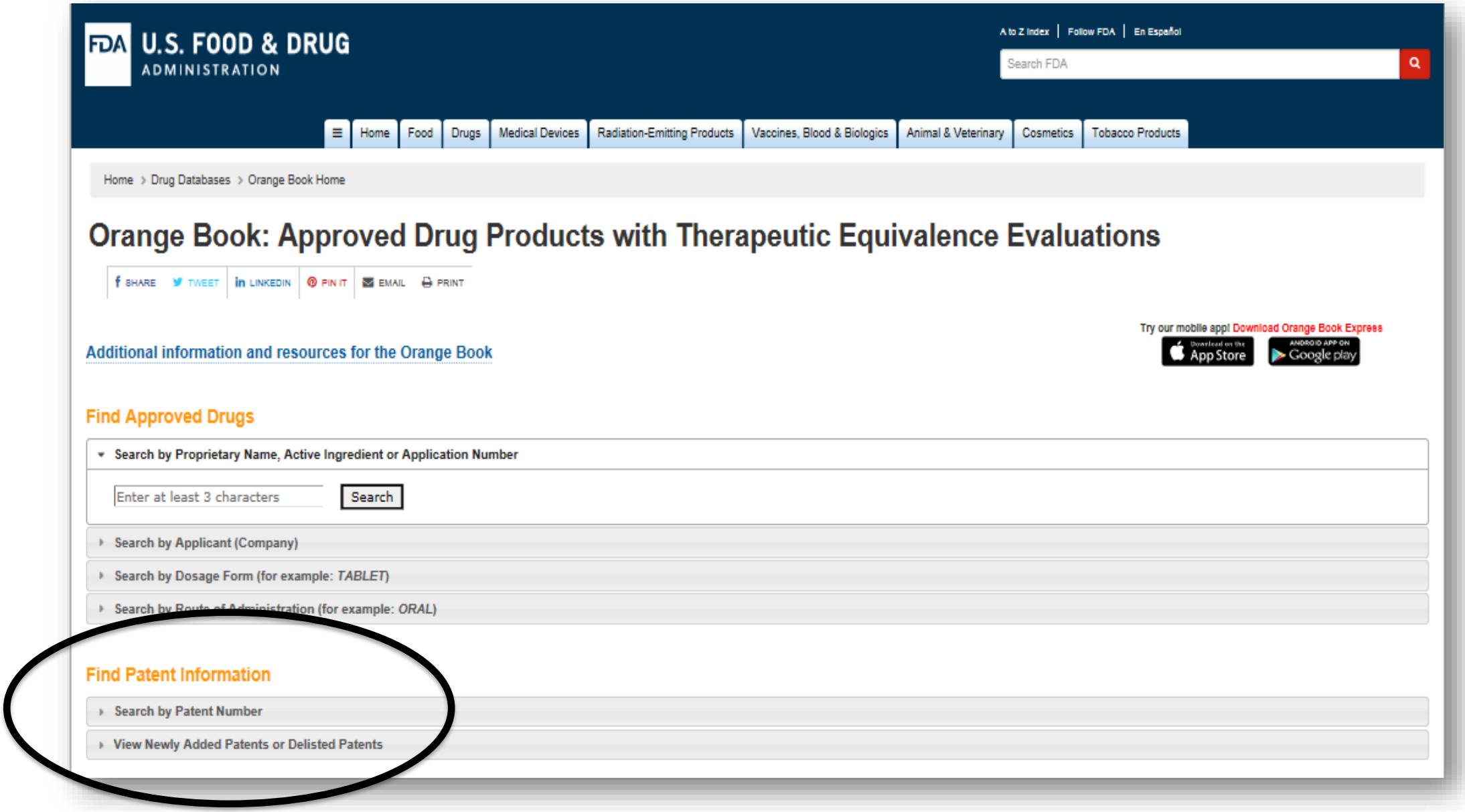
Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	6753445	07/09/2021	DS	DP	U-2619		09/17/2019
001	8071643	01/16/2029	DS	DP			09/17/2019
001	8153689	03/19/2028	DS	DP			09/17/2019

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
001	NCE	08/19/2024
001	NCE *GAIN	08/19/2029

Or: search by patent number, not drug product



Patent Information in Orange Book

Product 001
LEMUR ACETATE (RINGTAIL) SOLUTION 300MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	6753445	07/09/2021	DS	DP	U-2619		09/17/2019
001	8071643	01/16/2029	DS	DP			09/17/2019
001	8153689	03/19/2028	DS	DP			09/17/2019

- What patent data appears in the OB?
- Where does that information come from?
- When and how might that information change?

Source of OB Patent Information

- New Drug Application sponsors are **required** to submit for listing **patents** that protect their approved drug substance, drug product, or approved methods of use

- Timing: Upon filing of New Drug Application, amendment, or supplement **and again** within 30 days of approval.
  - Later-issued patents must be submitted within 30 days of issuance

OB Patent Listings – some caveats

- Orange Book users should not rely on an Orange Book patent listing to identify the complete range of patent claims that may be asserted by an NDA holder or patent owner.
- Not all patents potentially relevant to a drug product are required to be listed (eg: methods of making a drug product)
- Pending patent applications are not listed
- As of December 5, 2016, a patent that claims both the **drug substance** and the **drug product** (ie, eligible for listing on both bases) may be listed as drug substance or drug product alone (or both)

Submission of Patent Information

- Applicant *must* use FDA-provided form
  - Form 3542a before approval or Form 3542 within 30 days of approval or issuance of patent (for later-issuing patents)

- If there are no patents to list, that must be declared via a Form 3542/3542a submission:
  - "For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to 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."

Form 3542 highlights

For each patent submitted for the approved NDA or supplement referenced above, you must submit the information described below. If you are not submitting any patents for this NDA or supplement, complete the section above and sections 5 and 6.

1. GENERAL *(Please note: If 1.a is NOT entered, then section 5 later in form must be marked as "Yes" in its check box.)*

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner		
Address *(of Patent Owner)*	City	
State/Province/Region	Country	ZIP or Postal Code
FAX Number *(if available)*	Telephone Number	E-Mail Address *(if available)*

Click for additional set of 1.d. entries (includes all address and related contact items above). May be repeated. Add Section 1.d.

Drug Substance Listings

2. DRUG SUBSTANCE (ACTIVE INGREDIENT)		
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement? If yes, skip to Question 2.5.	☐ Yes	☐ No
2.2 Does the patent claim only a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? *(Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)*	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No

Drug Substance Listings

2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel?	☐ Not Applicable ☐ Yes ☐ No
FDA will not list the patent in the Orange Book as claiming the drug substance if: • **the answers to 2.1 and 2.2 are "No," or,** • **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,** • **the answer to 2.3 is "Yes" and there is no response to 2.4, or,** • **the answer to 2.5 or 2.6 is "Yes."** • **the answer to 2.7 is "No."**	

- FDA will not list as DS if the patent claims only:
  - Only a metabolite of AI
  - Only an intermediate of AI
  - Only a different polymorph *unless* certain certification made
  - A non-novel product, for a product-by-process patent

Drug Product Listings

3. DRUG PRODUCT (COMPOSITION/FORMULATION)			
3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?		☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?		☐ Yes	☐ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel?	☐ Not Applicable	☐ Yes	☐ No
FDA will not list the patent in the Orange Book as claiming the drug product if: • **the answer to question 3.1 is "No," or,** • **the answer to question 3.2 is "Yes," or,** • **the answer to 3.3 is "No."**			

- FDA will not list as DP if the patent claims only:
  - Only an intermediate
  - A non-novel product, for a product-by-process patent

Method of Use Listings

- Indicate whether patent claims one or more than one *approved* method(s) of use
- For each MOU listing, Form 3542 must identify sections of approved labeling describing that MOU
- For each MOU listing, applicant must provide a description of the approved use covered by the patent – the “use code”
  - Patent Use Codes are applicant-written
  - 250 character limit

Patent Use Codes

- A list of all Patent Use Codes appearing in OB can be accessed online (and in the PDF version)

- As of November 18, this list had 2,653 entries. Examples:

U-40	METHOD OF TREATMENT OF BURNS
U-41	METHOD OF TREATING CARDIAC ARRHYTHMIAS
U-42	ADJUVANT TREATMENT IN COMBINATION WITH FLUOROURACIL AFTER SURGICAL RESECTION IN PATIENTS WITH DUKES' STAGE C COLON CANCER
U-43	MANAGEMENT OF CHRONIC PAIN IN PATIENTS REQUIRING OPIOID ANALGESIA

“Newly Added Patents” and “Delisted Patents”

- Additions and changes since the last (monthly) Cumulative Supplement
- Patents that have been delisted since the most recent Annual Edition
- Facilitates monitoring

OB and Generic Drug Applications

- For every patent in OB, ANDA applicant must certify:
  - Patent has expired (Paragraph II certification)
  - Generic manufacturer will stay off market until patent expires (Paragraph III Certification)
  - Generic manufacturer believes that the listed patent is either invalid or would not be infringed by the proposed generic product (**Paragraph IV Certification**)
  - *[if patent information has not been filed: Paragraph I Certification]*

“Paragraph IV” Litigation

- If a Paragraph IV certification is made, applicant must notify NDA holder and patent owner of the certification once FDA has received the ANDA for review. §505(j)(2)(B)
- Notice must include statement of the factual and legal basis of the opinion of the ANDA applicant that the patent is invalid or will not be infringed.
- NDA holder can sue when it receives P-IV notice.
  - If lawsuit filed within 45 days of notice, ANDA approval generally stayed for 30 mos (some exceptions)
  - No lawsuit within 45 days of notice: FDA may approve ANDA following review process.

Challenges to OB Listings

- Presence of a patent in OB creates a regulatory hurdle – what can a potential generic applicant do if they believe a patent listing is incorrect?
- 21 CFR 314.53(f) sets out process for challenging listing
  - FDA mediates and discloses such challenges; does not itself substantively evaluate patent listings
  - Challenge is forwarded to NDA holder, who must respond by confirming, modifying, or removing the challenged patent listing
- Cumulative listing of OB patent listing disputes and their status/outcome available at:

https://www.fda.gov/drugs/drug-approvals-and-databases/orange-book-patent-listing-dispute-list

Patent Listing Disputes List

Patent Listing Disputes

Current through November 15, 2019

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
sodium oxybate	021196	Jazz Pharms	500 mg/mL	10213400	Method of Use	U-2499: Method of reducing adverse effects in patients suffering from excessive daytime sleepiness and/or cataplexy in narcolepsy who are concomitantly administered sodium oxybate and divalproex sodium	N/A	10/30/2019	10/29/2019	No Orange Book Changes
sodium oxybate	021196	Jazz Pharms	500 mg/mL	8772306, 9050302, 9486426	Method of Use	U-1532: Method of treating excessive daytime sleepiness and/or cataplexy in narcolepsy patients with sodium oxybate when divalproex sodium is concomitantly administered	N/A	10/30/2019	10/29/2019	No Orange Book Changes
sodium oxybate	021196	Jazz Pharms	500 mg/mL	8731963	Method of Use	U-1110: Method of treating a patient with a prescription drug using a computer database in a computer system for distribution	N/A	10/30/2019	10/29/2019	No Orange Book Changes
aberaterone acetate	202379	Janssen Biotech	250 mg, 500 mg	8822438	Disputes Not Related to Use Code	N/A	N/A	9/22/2019	9/19/2019	Patent Listing Updated
sodium oxybate	021196	Jazz Pharms	500 mg/mL	7668730, 7765106, 7765107, 7895059, 8457988, and 8589182	Disputes Not Related to Use Code	N/A	N/A	9/22/2019	9/19/2019	Patent Listing Updated
ramelteon	021782	Takeda Pharms USA	8 mg	10098866	Disputes Not Related to Use Code	N/A	N/A	7/18/2019	7/11/2019	No Orange Book Changes
fexofenadine hydrochloride	201373	Sanofi Aventis US	30 mg/5 mL	8933097	Disputes Not Related to Use Code	N/A	N/A	6/15/2019	6/12/2019	Patent Listing Updated

https://www.fda.gov/drugs/drug-approvals-and-databases/orange-book-patent-listing-dispute-list

Biological Products

- OB lists drug products approved under §505 of the FDCA
- **Biological products** licensed under §351 of the Public Health Service Act are *not* listed in the OB
  - § 351 defines a biological product as a "virus, therapeutic serum, toxin, antitoxin, **vaccine**, blood, blood component or derivative, allergenic product, or analogous product, … applicable to the prevention, treatment, or cure of a disease or condition of human beings."
  - FDA regulations and policies have established that biological products include blood-derived products, **vaccines**, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and **most protein products**.

The “Purple Book”

- The Purple Book lists biological products licensed by FDA under the PHS Act
  - Including any *biosimilar* and *interchangeable* biological products
- Some similarities in purpose, but differences in content
- The Purple Book does *not* include patent information
  - BPCIA sets forth a “patent dance” for biologic follow-on applicants
- Published as PDFs updated periodically

The Off-Patent/Off-Exclusivity List

- 2017 initiative to encourage generic drug development

- Goal: highlight branded drugs with no listed patents or exclusivities and no approved generic
  - Encourage development and submission of ANDAs in markets with limited competition
  - Facilitate use of Orange Book data for this purpose

OP/OE List: Scope

- Approved new drug application (NDA, §505) products
  - for which no patents or exclusivities are listed, ***and***
  - for which FDA has not approved an abbreviated new drug application (ANDA) referencing that NDA product.

- Does not include biologics licensed under §371

- Updated periodically (thus far, every 6 months)

OP/OE List

- List is separated into three sections:
  - Part I: drug products for which FDA could immediately receive an ANDA* for review without prior discussion.
  - Part II: drug products for which ANDA development or approval may raise potential legal, regulatory, or scientific issues that should be addressed with the Agency prior to considering submission of an ANDA.
  - Appendix: NDA drug products that were removed from Part I or Part II of the list because one or more ANDAs referencing such NDA drug products have been approved since the previous list publication.

Accessing the OP/OE List

- https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/list-patent-exclusivity-drugs-without-approved-generic

Current List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic

- June 2019 List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic PDF | Excel

Previous Lists of Off-Patent, Off-Exclusivity Drugs without an Approved Generic

- December 2018 List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic PDF | Excel
- June 2018 List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic PDF | Excel
- December 2017 List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic PDF | Excel
- June 2017 List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic PDF | Excel

- PDF version includes the methodology
- First edition was based on active ingredients, not drug products

OP/OE List: Excerpts

Part I

June 2019: 329 entries

Ingredient	Approved NDA	Dosage Form
ACETAMINOPHEN	N204767	SOLUTION
ACETYLCHOLINE CHLORIDE	N020213	FOR SOLUTION
ACRIVASTINE; PSEUDOEPHEDRINE HYDROCHLORIDE	N019806	CAPSULE

Part II

June 2019: 174 entries

Ingredient	Approved NDA	Dosage Form
ACETOHYDROXAMIC ACID	N018749	TABLET
ACYCLOVIR	N202408	OINTMENT
ALBUMIN IODINATED I-125 SERUM	N017836	INJECTABLE
ALBUMIN IODINATED I-131 SERUM	N017837	INJECTABLE
ALITRETINOIN	N020886	GEL
ALPROSTADIL	N020649	INJECTABLE
ALPROSTADIL	N021212	INJECTABLE

OP/OE List: Comments

Appendix

Ingredient	Approved NDA	Dosage Form
ACYCLOVIR	N021478	CREAM
AMINOCAPROIC ACID	N015197	TABLET
ERYTHROMYCIN ETHYLSUCCINATE	N050207	GRANULE
HYDROXYPROGESTERONE CAPROATE	N021945	SOLUTION
LOTEPREDNOL ETABONATE	N020583	SUSPENSION/DROPS
METHYLPREDNISOLONE	N011153	TABLET
MIFEPRISTONE	N020687	TABLET
NAFTIFINE HYDROCHLORIDE	N019356	GEL
PYRIDOSTIGMINE BROMIDE	N015193	SYRUP
TOREMIFENE CITRATE	N020497	TABLET
VIGABATRIN	N020427	TABLET

- Appendix lists products removed from prior OP/OE because at least one ANDA is now approved
  - June 2019 Appendix: 11 products
- Reminder: OP/OE relies on OB patent listings

Orange Book – Key Summary

- FDA-maintained listing of drugs approved under §505
- Resource for information on drug marketing status, therapeutic equivalence and substitutability, and patent and exclusivity data.
- Relied upon by applicants submitting an ANDA to identify patents that need to be certified to in a generic drug application

- Patent information in the OB is provided by sponsors, not evaluated by FDA
- FDA has administrative role only in challenges to OB patent listings

Acknowledgements

orangebook@fda.hhs.gov

https://www.fda.gov/drugs/drugapprovals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book

https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/list-patent-exclusivity-drugs-without-approved-generic