FDA Drug Topics: *Orange Book:* Frequently Asked Questions and Answers

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- The Orange Book at 40: A valued FDA resource continually enhanced by user input

Purpose

- The purpose of this presentation is to answer common questions about the FDA's Orange Book

Objectives

At the conclusion of the webinar the attendee should be able to:

- Utilize the Orange Book to identify therapeutically equivalent products
- Identify the regulatory requirements for submission of patent information to the FDA
- Recognize the statutory requirements for the movement of drug products between the active and discontinued sections of the Orange Book and the Orange Book timing for publication
- Employ the Orange Book website to locate relevant regulatory information

WHAT IS THE ORANGE BOOK?

Orange Book – Background

The Orange Book is an FDA publication mandated under section 505(j)(7)(A) of the Federal Food, Drug, & Cosmetic Act (FD&C Act) which:

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

Orange Book - Background

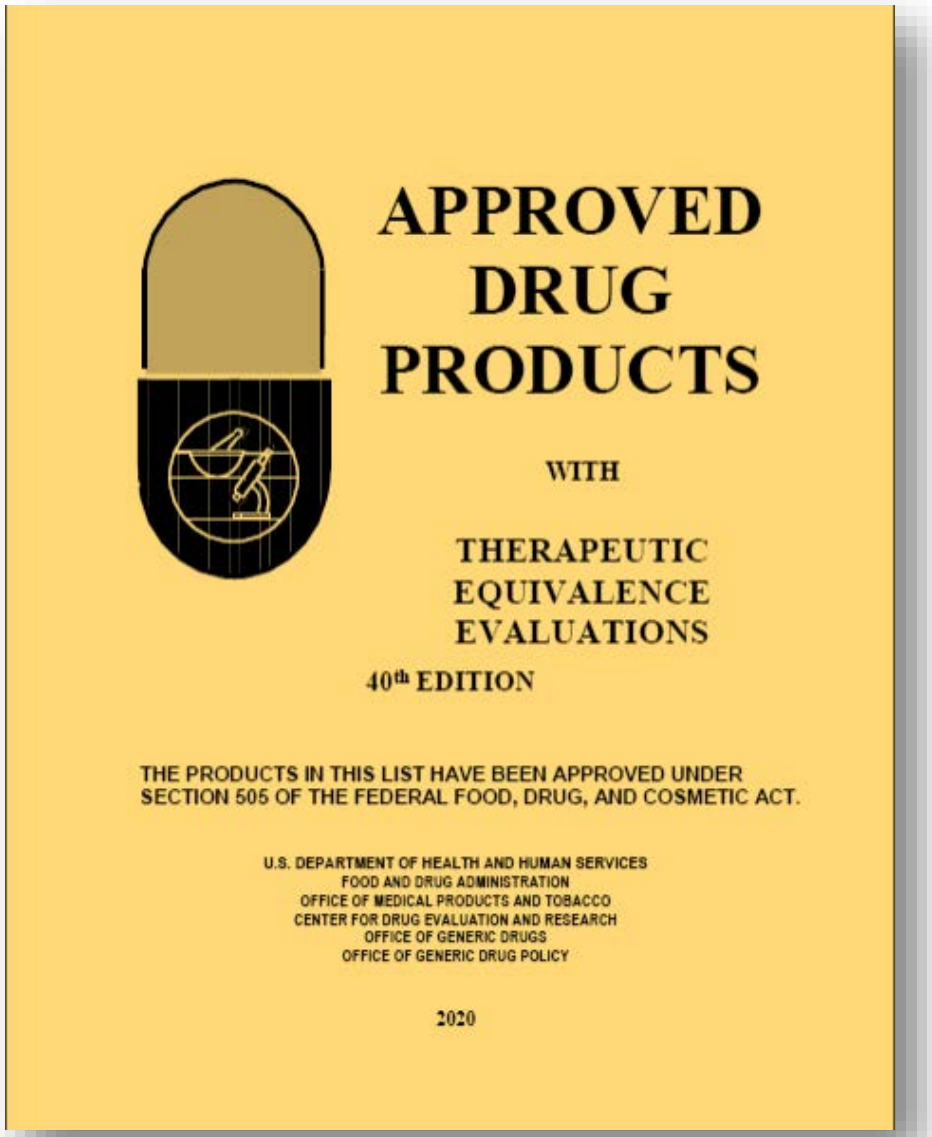
"…The Food and Drug Administration (FDA) proposes to amend its public information regulations to make available a list of all approved drug products, together with therapeutic evaluations of listed products that are available from more than one manufacturer (multisource)…"

- *Proposed Rule, Therapeutically Equivalent Drugs*, 44 Fed. Reg. 2932, 2953 (January 12, 1979)

What is the Orange Book?

Approved Drug Products with Therapeutic Equivalence Evaluations

- *Final Rule, Therapeutically Equivalent Drugs; Availability of List*, 45 Fed. Reg. 72582, 72608 (October 31, 1980)



Orange Book – Main Sections

- Prescription Drug Product List
- Over-the-Counter (OTC) Drug Product List
- Discontinued Drug Product List
- Drug Products with Approval under Section 505 of the Act

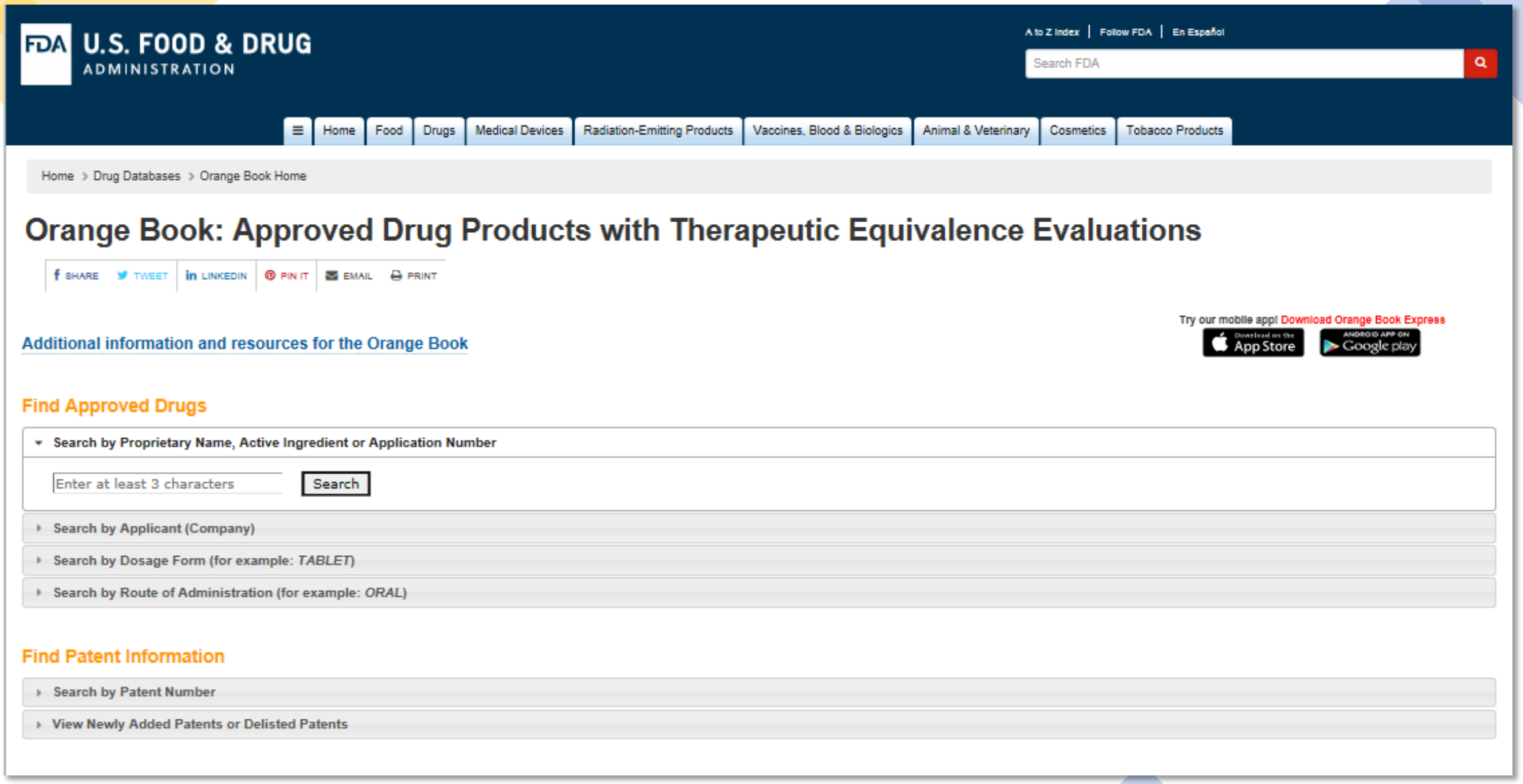
Orange Book – Other Information Included

- Orange Book Preface
  - Introduction to the Orange Book
  - Contains:
    - Background and Relevant History
    - Content and Exclusion
    - General Policies
  - *Orange Book Annual Edition*
  - *Orange Book Cumulative Supplement*
- Patent Information
- Exclusivities

Orange Book – Does Not Include

- Pre-1938 drugs that are not subject to pre-market clearance procedures
- Pre-1962 drug products subject to the Drug Efficacy Study Implementation (DESI) process for which the DESI proceeding is not yet complete
- Unapproved marketed products
- Approved drugs which discontinued marketing prior to 1979
- Tentatively approved drugs

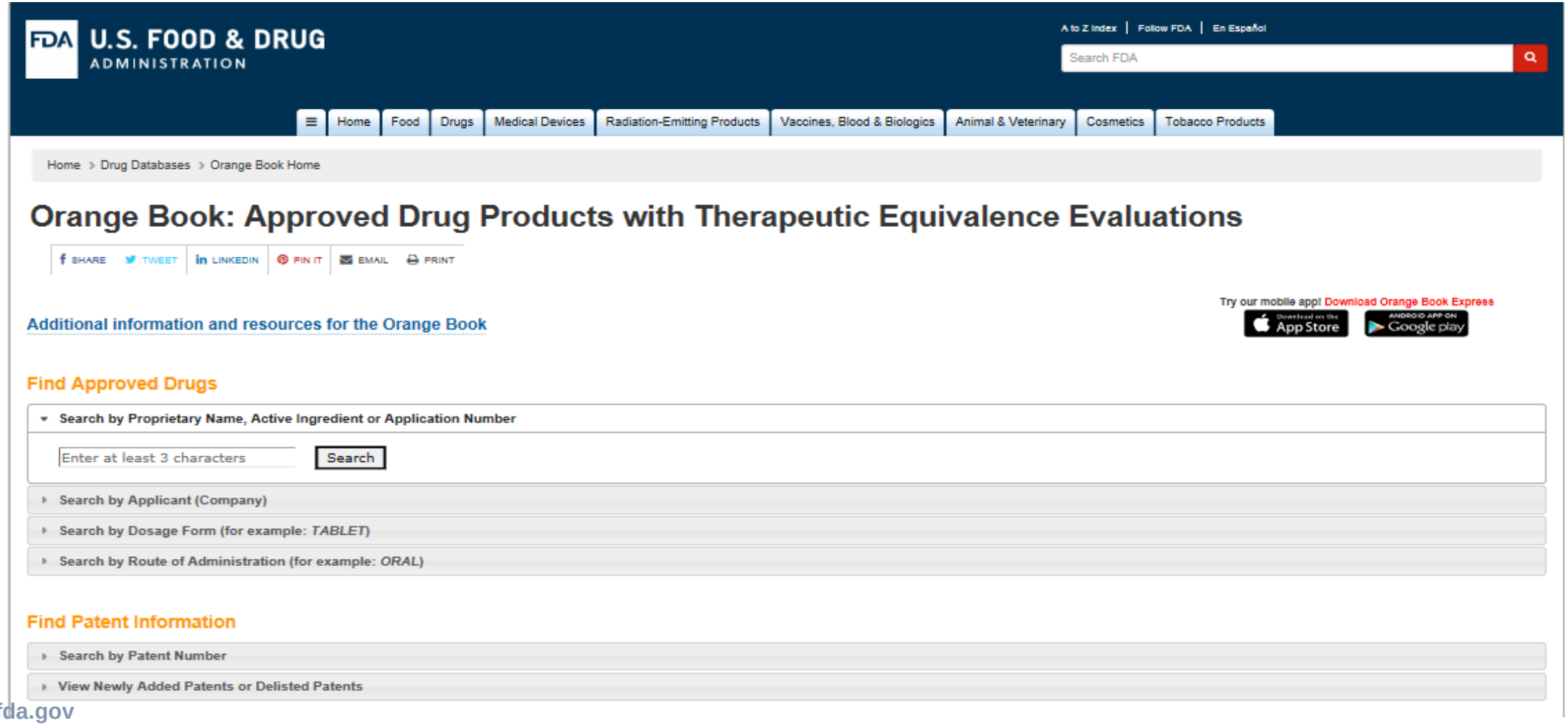
Available on the internet: www.fda.gov/orangebook



HOW TO FIND INFORMATION

Orange Book – How to find Information

- **How do I search for drugs in the Orange Book?**



Orange Book – How to find Information

- **How do I search for drugs in the Orange Book?**
  - Example Drug Product Search in the Orange Book

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	A
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	300MG; 50MG; 40MG; 30MG				N
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			N
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A075929	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			V IN
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	- W/ CODEINE	N020232	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB	RLD	RS	A IN
DISCN	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076528	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG				A

Orange Book – How to find Information

- **What does “RLD” mean?**

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	A
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	300MG; 50MG; 40MG; 30MG				N
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			N
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A075929	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			V IN
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	- W/ CODEINE	N020232	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB	RLD	RS	A IN
DISCN	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076528	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG				A

Orange Book – How to find Information

- **What does “RS” mean?**

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	A
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	300MG; 50MG; 40MG; 30MG				N
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			N
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A075929	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			V IN
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	- W/ CODEINE	N020232	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB	RLD	RS	A IN
DISCN	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076528	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG				A

General Questions – How to find Information

- **I want drug information no longer found in the Orange Book. How do I go about getting it?**
  - Requests for previous editions of the Orange Book or an Orange Book Data File should be made under the Freedom of Information Act. Requests should be submitted either online via https://www.fda.gov/regulatory-information/freedom-information/how-make-foia-request or in writing to FDA's Freedom of Information Staff at the following address:

    FDA/Division of Freedom of Information 130
    Office of the Executive Secretariat, OC 131
    5630 Fishers Ln., Rm. 1035
    Rockville, MD 20857

General Questions – How to find Information

- **How often is the Orange Book updated?**
  - Daily
    - Generic drug approvals and patents
  - Bi-Monthly Updates 

    - New drug approvals, exclusivity, ownership changes, market status, other (i.e., changes related to active ingredient, strength, dosage form, route, therapeutic equivalence code, trade name, reference standard)
  - Annually
    - Annual Orange Book Edition Publication

General Questions – How to find Information

- **Why can't I find insulin products in the Orange Book?**
  - On March 23, 2020, the Biologics Price Competition and Innovation Act of 2009 requires that an approved application for a biological product under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) shall be deemed to be a license for the biological product under section 351 of the Public Health Service Act (PHS Act)
  - FDA removed from the Orange Book the listings for "biological products" that have been approved in applications under section 505 of the FD&C Act because these products are no longer "listed drugs" (see section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009)

General Questions – How to find Information

- **Why can't I find insulin products in the Orange Book? (*cont'd*)**
  - To enhance transparency, FDA is making available an archival copy of the Orange Book as of March 20, 2020, the last working day before the March 23, 2020 transition date
  - This archival copy contains information available in the Orange Book as of the morning of March 20, 2020, and generally includes information, such as patent and exclusivity information, for "biological products" that have been approved under section 505 of the FD&C Act as of March 19, 2020

ORANGE BOOK: MARKETING STATUS

Orange Book– Marketing Status

- **When does a newly approved drug product appear in the Orange Book?**
  - Abbreviated New Drug Applications (ANDA) will generally appear in the active section of the Orange Book either the same day of approval or within the next business day
  - Newly approved New Drug Applications (NDA) applications will generally appear with the next bi-monthly update to the Orange Book
    - Note: If the applicant holder notifies FDA that it does not intend to market the drug upon approval the product will appear in the discontinued section of the Orange Book

Orange Book– Marketing Status

- **When does a newly approved drug product appear in the Orange Book? (*cont'd*)**
  - *Notification of drug not available for sale*
    - Section 506I(b) of the FD&C Act, requires the applicant to provide written notification to FDA within 180 days of the date of the approval

Orange Book– Marketing Status

- **When is a product moved to the discontinued section of the Orange Book?**
  - *Notification of withdrawal from sale*
    - NDA and ANDA holders are required to provide a written notification to FDA 180 days prior to withdrawing an approved drug product from sale
      - If it is not practicable to submit the notification 180 days before withdrawing the drug product from sale, that submission should be made “as soon as practicable but not later than the date of withdrawal” from sale

Orange Book– Marketing Status

- **When is a product moved to the discontinued section of the Orange Book? *(cont'd)***
  - *Section 506I(d) of the FD&C Act*
    - Authorizes FDA to move the NDA and/or ANDA holder's drug products from the active section of the Orange Book to the discontinued section if an NDA or ANDA holder fails to submit any of these three marketing status notifications

Orange Book– Marketing Status

- **How does an applicant have a drug product moved from the the discontinued section of the Orange Book to the active section?**

  - Notification of Commercial Marketing

  - When an NDA or ANDA holder intends to commence commercial marketing of a drug for which the holder has previously submitted a notification that the drug was not available for sale, FDA recommends that the NDA or ANDA holder notify FDA 30-60 days before the anticipated launch date, which generally is the date the drug product will be introduced or delivered for introduction into interstate commerce, but no later than the date commercial marketing is commenced

THERAPEUTIC EQUIVALENCE

Orange Book – Therapeutic Equivalence Code

- **What are therapeutic equivalents?**
  - *Therapeutic equivalents* (TE) are approved drug products that are **pharmaceutical equivalents** for which **bioequivalence** has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

Orange Book – Therapeutic Equivalence Code

- **What are therapeutic equivalents? (*cont'd*)**
  - **Pharmaceutical equivalents (PE)ǂ**
    Drug products in:
    - *Identical* dosage forms and route(s) of administration
    - *Identical* amounts of the active drug ingredient
    - *Identical* strength (or concentration)
  - **Bioequivalence(BE)ǂ** – absence of a significant difference in the rate and extent to which the drug becomes available at the site of action
    - Same clinical effect and safety profile under the conditions specified in the labeling
  - TE = PE + BE for the conditions specified in the labeling

- ǂ *See 21 CFR 314.3(b) for full definitions*

Orange Book – Therapeutic Equivalence Code

- **What are the Therapeutic Equivalence Codes in the Orange Book?**
  - The therapeutic equivalence codes in the Orange Book reflect FDA's evaluation of whether multisource prescription drug products listed in the Orange Book and approved under Section 505 of the FD&C Act are therapeutically equivalent to other pharmaceutically equivalent products.
  - These evaluations are presented in the form of code letters that indicate the basis for the evaluation made.

Orange Book – Therapeutic Equivalence Code

- **What are the Therapeutic Equivalence Codes in the Orange Book? *(cont'd)***
  - Substitutable if "A" rated
    - "A" ratings—AB, AA, AN, AO, AP, AT where the second letter provides additional information such as dosage form
    - "AB" – (most common)
  - Not substitutable if "B" rated
    - Not determined to be therapeutically equivalent
    - BX most common

Orange Book – Therapeutic Equivalence Code

- **What are the Therapeutic Equivalence Codes in the Orange Book? *(cont'd)***

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	A
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	300MG; 50MG; 40MG; 30MG				N
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			N
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A075929	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			V IN
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	W/ CODEINE	N020232	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB	RLD	RS	A IN
DISCN	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076528	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG				A

Orange Book – Therapeutic Equivalence Code

- **What are the Therapeutic Equivalence Codes in the Orange Book? *(cont'd)***

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	Appl
RX	SUMATRIPTAN SUCCINATE	ALSUMA	N022377	INJECTABLE	SUBCUTANEOUS	EQ 6MG BASE/0.5ML (EQ 12MG BASE/ML)	BX		MER PHA
RX	SUMATRIPTAN SUCCINATE	SUMAVEL DOSEPRO	N022239	INJECTABLE	SUBCUTANEOUS	EQ 4MG BASE/0.5ML (EQ 8MG BASE/ML)	BX	RLD	END
RX	SUMATRIPTAN SUCCINATE	SUMAVEL DOSEPRO	N022239	INJECTABLE	SUBCUTANEOUS	EQ 6MG BASE/0.5ML (EQ 12MG BASE/ML)	BX	RLD	END
RX	SUMATRIPTAN SUCCINATE	IMITREX	N020080	INJECTABLE	SUBCUTANEOUS	EQ 6MG BASE/0.5ML (EQ 12MG BASE/ML)	AP	RLD	GLA

Orange Book – Therapeutic Equivalence Code

- **How do I use the Orange Book to find an approved generic drugs?**

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	A
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	300MG; 50MG; 40MG; 30MG				N
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			N
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PATENT INFORMATION

Orange Book – Patent Information

- **What is the difference between patents and exclusivity?**
  - Patents are a property right granted by the United States Patent and Trademark Office anytime during the development of a drug and can encompass a wide range of claims
  - Currently, the term of a new patent is 20 years from the date on which the application for the patent was filed in the United States

Orange Book – Patent Information

- **What is the difference between patents and exclusivity? (cont'd)**
  - Exclusivity refers to a period of limited protection from generic competition, as provided for in the FD&C Act and Administered by FDA
    - Provides the holder of an approved drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product

Orange Book – Patent Information

- **What is the difference between patents and exclusivity? (cont'd)**
  - Differing lengths of exclusivity periods, depending on the type of exclusivity at issue
    - Orphan Drug – 7 years
    - New Chemical Entity – 5 years
    - Generating Antibiotic Incentive Now- 5 years
    - New Clinical Investigation- 3 years
    - Pediatric Exclusivity – 6 months
    - Patent Challenge and Competitive Generic Therapy exclusivity -180 days

Orange Book – Patent Information

- **How does an NDA holder provide patent information for listing in the Orange Book?**
  - Patents are required to be submitted on Form ***FDA 3542*** for Orange Book listing
  - Types of Patents for Which Information Must Be Submitted
    - **Drug Substance (active ingredient)**
    - **Drug Product (formulation/composition)**
    - **Method-of-Use (approved)**
  - Use of the forms can help to ensure complete information is submitted

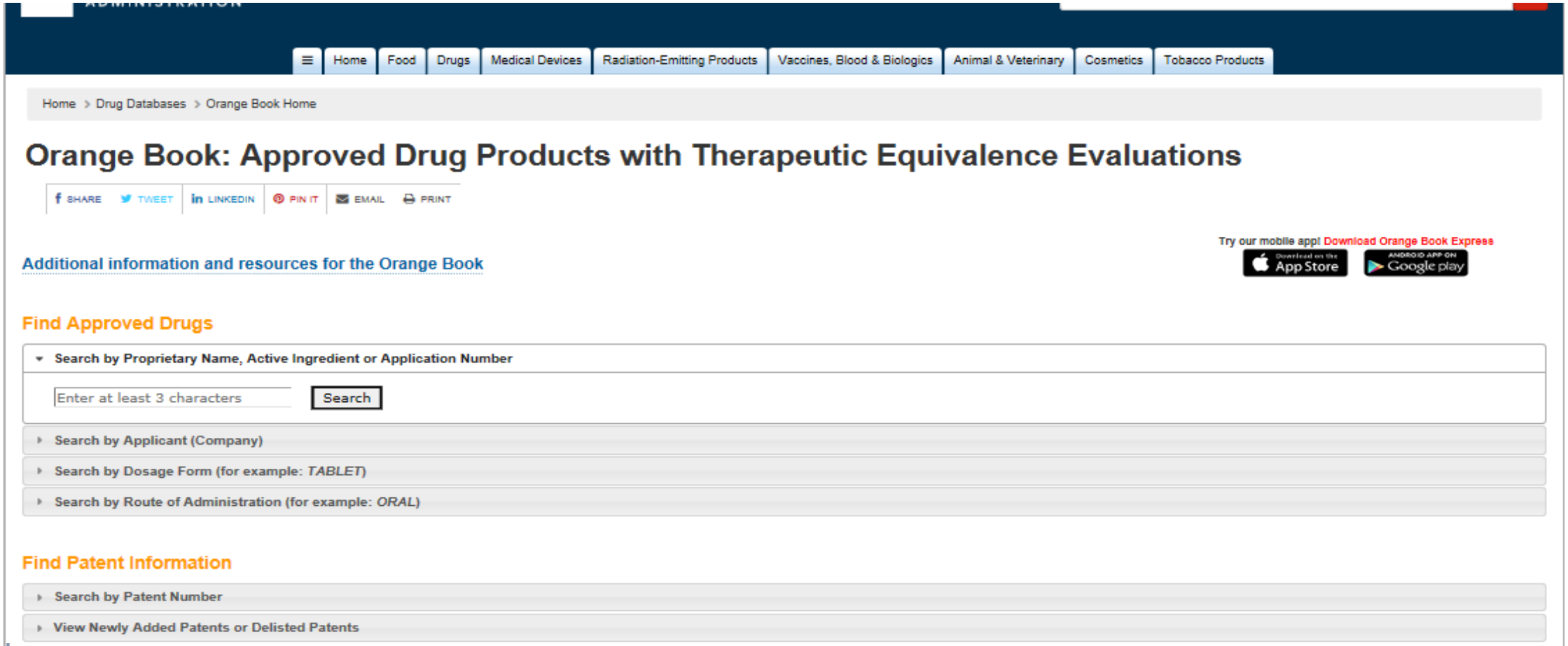
Orange Book – Patent Information

- **Where can I find regulations related to the submission of patent information to FDA?**

  - General requirements for the submission of patent information to the FDA can be found in the Code of Federal Regulations (CFR) under 21 CFR 314.53.

Orange Book – Patent Information

- **How do I search for patent information in the Orange Book?**



Orange Book – Patent Information

- **How do I search for patent information in the Orange Book? (*cont'd*)**

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
002	6403569	04/28/2020			U-449		
002	6403569*PED	10/28/2020					
002	6794370	05/01/2020			U-606		
002	6794370*PED	11/01/2020					

Orange Book – Patent Information

- **How does an NDA holder ensure that Form FDA 3542 (Patent Information Submitted Upon and After Approval of an NDA or Supplement) is timely filed?**
  - For patent information to be considered timely filed, a Form FDA 3542 must be submitted to the NDA within 30 days after the date of approval of the NDA or supplement or, for patents issued after the date of approval, within 30 days of issuance, for each patent that claims the drug substance (active ingredient), drug product (formulation or composition), and/or an approved method of using the approved drug product

Orange Book – Patent Information

- **How does an NDA holder ensure that Form FDA 3542 (Patent Information Submitted Upon and After Approval of an NDA or Supplement) is timely filed? (*cont'd*)**
  - *Correction of Errors or Omissions*
    - Under the terms of the regulation, 314.53(c)(2)(ii), to be considered timely filed as of the date of the original submission of patent information, the NDA holder must submit an acceptable Form FDA 3542 within 15 days of FDA's original notification

Orange Book – Patent Information

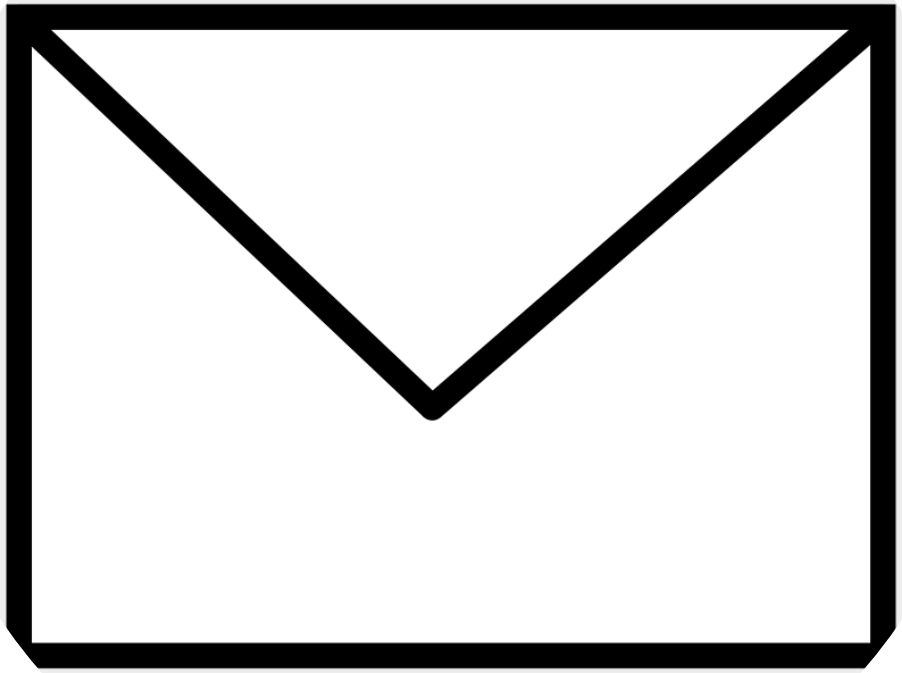
- **Can a patent listing be disputed?**
  - A person other than the NDA holder can dispute the accuracy or relevance of patent information published in the Orange Book
  - Refer to 21 CFR 314.53(f)(1) for more information regarding this process

In Summary

- The Orange Book contains therapeutic equivalence evaluations for approved multisource prescription drug products, which serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education on drug product selection and to foster containment of healthcare costs
- The FD&C Act and FDA regulations require NDA and ANDA holder to notify the Agency of the marketing status of drug products approved under NDAs and ANDAs, and also require the submission of certain patent information by NDA holders
- FDA is continuing its efforts to maximize the usefulness of the Orange Book for its stakeholders, including by providing greater clarity around frequently asked questions regarding the Orange Book

References

- Draft guidance for industry *Orange Book Questions and Answers Guidance for Industry* (May 2020)
- Orange Book Preface (40th Edition 2020) available at https://www.fda.gov/media/71474/download
- *Orange Book website*. (2020, October), available at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm



For Questions – Contact Us:

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