U.S. FOOD & DRUG ADMINISTRATION

The Orange Book

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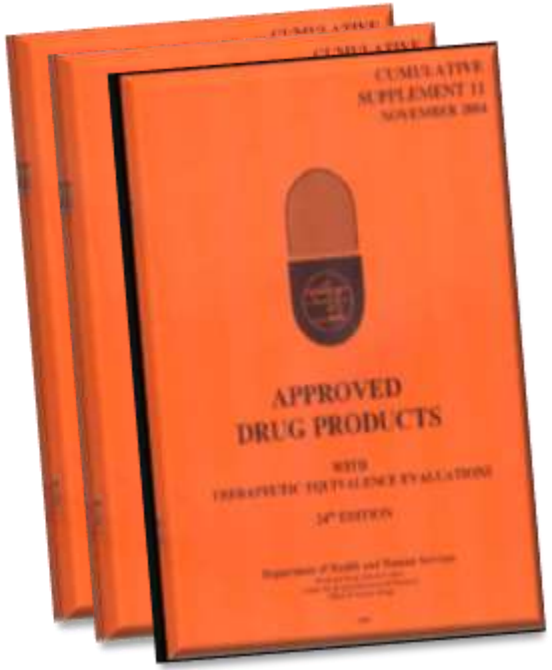
Topics for Discussion

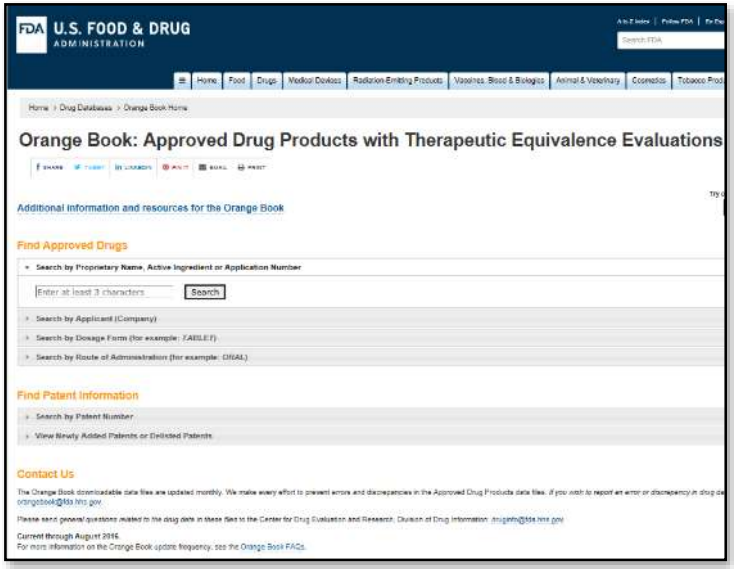
- Provide a brief overview of the FDA's Orange Book
- Explain key aspects of Drug Product Listings in the Orange Book
- Describe FDA's role with respect to marketing protections (i.e., patents and exclusivities)

Background and History

- Most states adopted regulations to encourage drug product substitution to contain costs
- Mandated list of ***safe*** and ***effective*** drug products approved under Section 505(c) and 505(j) of the Federal Food Drug and Cosmetic Act (FD&C Act)
- Contains drug product substitutability information

Available Formats





Key Sections

- Orange Book Preface
- Drug Product Lists
  - Prescription
  - Over-the-Counter (OTC)
  - Discontinued
- Patents and Exclusivity

DRUG PRODUCT LISTS

Therapeutic Equivalence (TE)

- TE codes indicate substitutability between products

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076660	CAPSULE	ORAL	300MG; 50MG; 40MG; 30MG	
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076660	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076929	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB
RX	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	FIORICET W/ CODEINE	N020232	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB
DISCN	ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076628	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	

TE = PE + BE for same use

- Pharmaceutical equivalents (PE)[‡] contain the same:
  - Active drug ingredient
  - Dosage form and route(s) of administration
  - Strength (or concentration)
- Bioequivalent (BE)[‡] – absence of a significant difference in the rate and extent of drug available at the site of action
- Same clinical effect and safety profile under the conditions specified in the labeling

[‡] *See 21 CFR 314.3 for full definitions*

Therapeutic Equivalence (TE) Codes

- "A" ratings: e.g., AB (most common)
  - Therapeutically equivalent – May substitute
  - Actual or potential BE problems resolved with studies
- "B" ratings: e.g., BX (most common)
  - Data insufficient to determine TE – Not recommended for substitution

Reference Listed Drug (RLD)

- Listed drug an applicant relies upon in seeking approval of its ANDA (*21 CFR 314.3(b)*)

Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS
ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	300MG; 50MG; 40MG; 30MG			
ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB		
ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A075929	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB		
ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	FIORICET W/ CODEINE	N020232	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB	RLD	RS

Reference Standard (RS)

- Used by ANDA applicants for conducting *in vivo* BE studies *(See Draft Guidance- Referencing Approved Drug Products in ANDA Submissions)*

Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS
ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	300MG; 50MG; 40MG; 30MG			
ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ACETAMINOPHEN, CAFFEINE AND CODEINE PHOSPHATE	A076560	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB		
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Orange Book: Selecting a RS

- Generally assigned to highest strength
- Generally assigned to the generic market leader when innovator RLD is unavailable

Marketing Status Notifications

Marketing Status	Prominently Identified As
Withdrawal From Sale	ADMINISTRATIVE CHANGE / NOT AVAILABLE FOR SALE
Drug Not Available for Sale	
Marketing Begins	ADMINISTRATIVE CHANGE / NOTIFICATION OF COMMERCIAL MARKETING

PATENTS AND EXCLUSIVITY

Types of Patents Listed

1. **Drug Substance** (ingredient) - includes polymorphs
2. **Drug Product** (approved formulation/composition) - includes novel product by process
3. **Method of Use** (approved indication)

Patent Listings: Form FDA 3542

- Required to be submitted for Orange Book listing to ensure only specific types of patents are listed
- Submitted after approval of original NDAs and supplements
- Forms ensure that complete information is submitted

Orange Book: Patent Listings

Patent and Exclusivity for: N202293

Product 001
DAPAGLIFLOZIN (FARXIGA) TABLET 5MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code
001	6414126	10/04/2020	DS	DP	U-493 U-2139
001	6515117	10/04/2020	DS	DP	U-493 U-2139

Exclusivities

NDA Exclusivities

- New Chemical Entity
- New Clinical Investigation
- Orphan
- Pediatric
- GAIN

ANDA Exclusivities

- Patent Challenge
- Competitive Generic Therapy

Orange Book: Exclusivity Listings

Patent and Exclusivity for: N210166

Product 001
PRUCALOPRIDE SUCCINATE (MOTEGRITY) TABLET EQ 1MG BASE

Exclusivity Data

Product No	Exclusivity Code
001	NCE

Conclusion

- The Orange Book is:
  - A list of drugs approved under Section 505(c) and 505(j) of the Federal Food, Drug, and Cosmetic Act
  - Critical in determining when approved generic drugs can be substituted for the innovator product
  - The only definitive source for Therapeutic Equivalence (TE), Reference Listed Drug (RLD), Reference Standard (RS) data, and Patent and Exclusivity data

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