THE ORANGE BOOK:
AN OVERVIEW

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Bottom Line Up Front (BLUF):

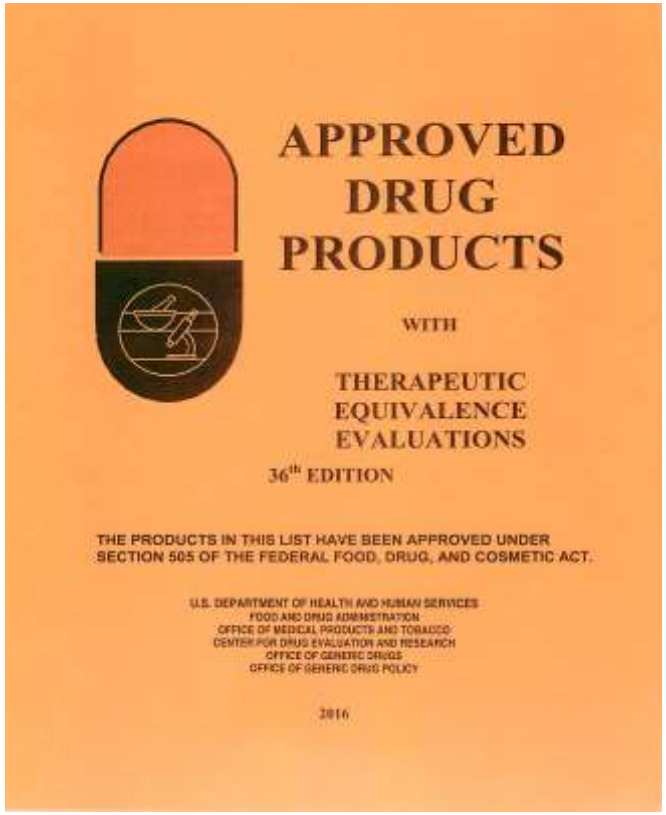
- The Orange Book is a resource which identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and related patent and exclusivity information.

Topics for Discussion

- Provide a history and overview of the FDA's Orange Book
- Explain the content of the Orange Book
- Describe how to identify and understand drug products, patent, and exclusivity information in the Orange Book.

About the Orange Book

Approved Drug Products with Therapeutic Equivalence Evaluations



Background and History

- In the late 1970s, to contain drug costs, virtually every state adopted laws and/or regulations that encouraged the substitution of drug products
- The Agency recognized that it would be beneficial to provide a single list of all prescription drug products that were approved by FDA as both safe and effective, along with therapeutic equivalence determinations for multisource prescription products

Overview of the Orange Book

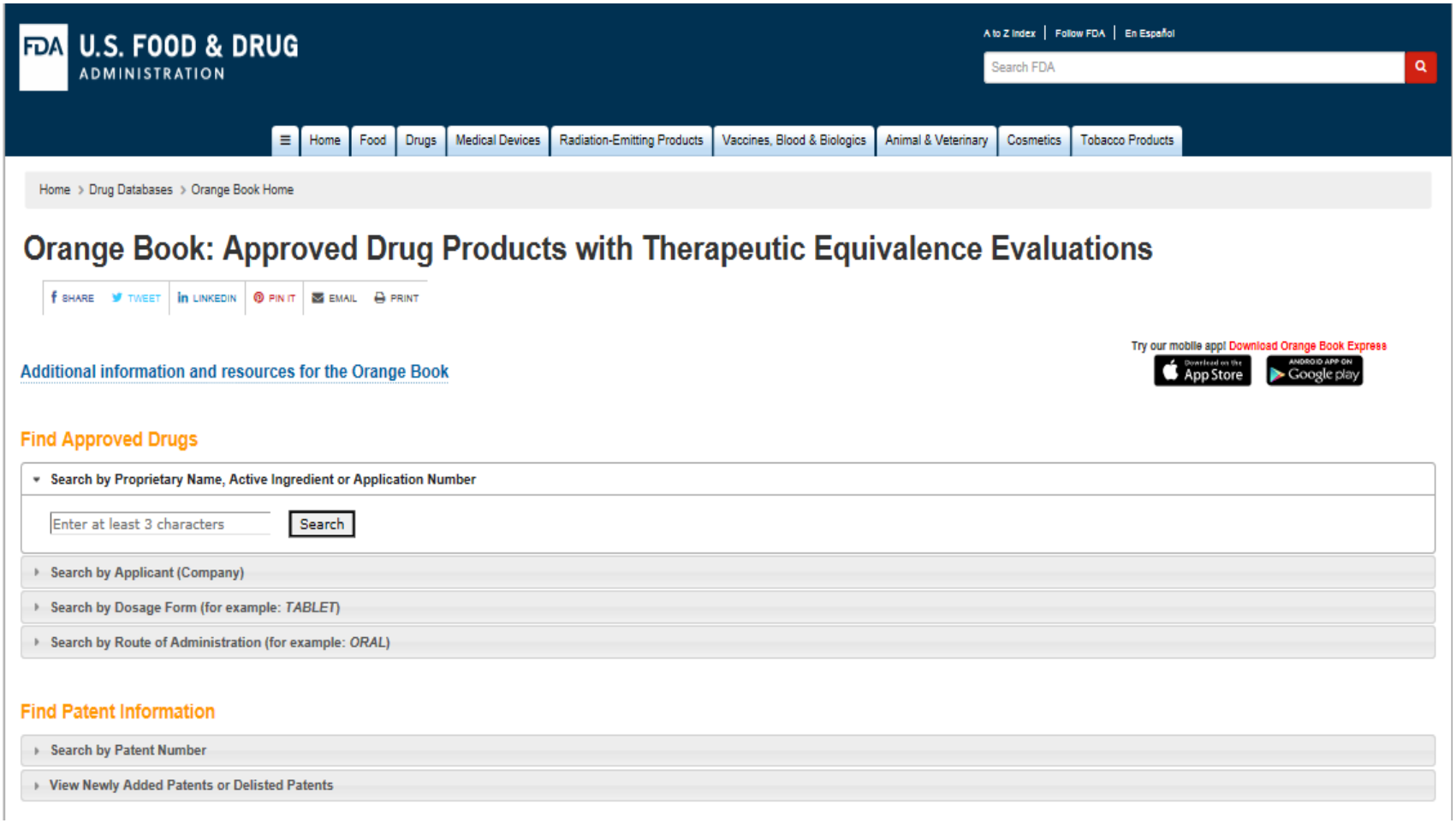
- Fulfills a mandate to list drug products approved as ***safe*** and ***effective*** under section **505(c)** of the Federal Food, Drug, and Cosmetic Act

- Contains substitutability information for approved drug products

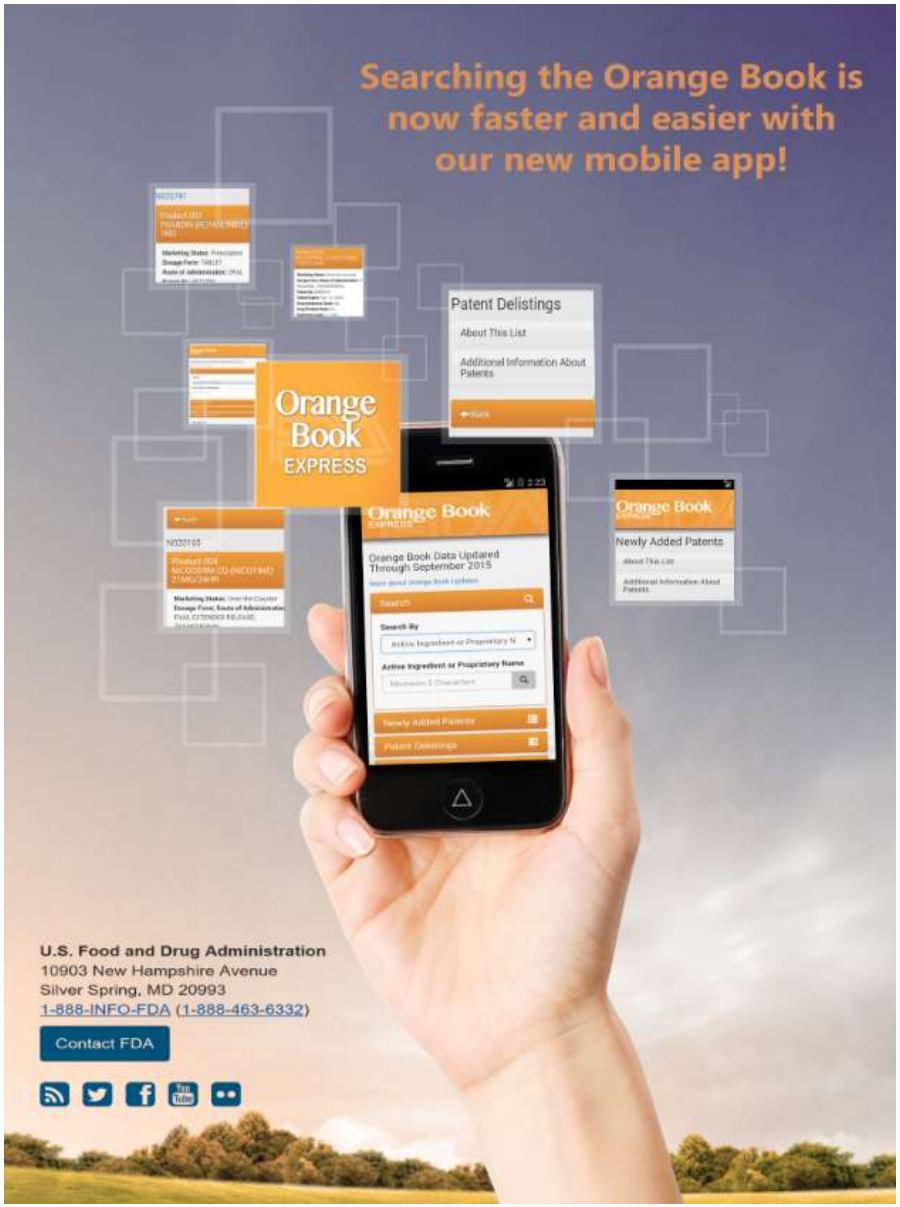
Orange Book: Available Formats

Orange Book: Available Formats

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



Orange Book: Available Formats



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ANDROID APP ON Google play

Information Updates to the Orange Book

- Daily (Website and App)
  - Generic Drug approvals & Patents
- Monthly (Website, App, and Publication)
  - NDA approval, Exclusivity, Applicant Name Changes, Active Ingredient, Discontinued, Strength, Dosage Form, Route, TE Code, Trade Name
- Annually (Website, App, and publication)
  - Annual Orange Book Edition Publication

Orange Book Key Sections

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

Orange Book: Information Not Included

- Pre-1938 drugs that are not subject to pre-market clearance procedures
- Drug products marketed between 1938 and 1962 that have not completed the DESI process
- All unapproved marketed products
- Approved drugs that had discontinued marketing prior to 1979.

Sample Drug Product List

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Ho
RX	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ASPIRIN, CAFFEINE AND CODEINE PHOSPHATE	A203335	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			MAYNE PHA
RX	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ASPIRIN, CAFFEINE, AND CODEINE PHOSPHATE	A074951	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			JEROME STE INC
RX	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ASPIRIN, CAFFEINE, AND CODEINE PHOSPHATE	A075231	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			NEXGEN PH
RX	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	FIORINAL W/CODEINE	N019429	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB	RLD	RS	ALLERGAN S
DISCN	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ASPIRIN, CAFFEINE, AND CODEINE PHOSPHATE	A074359	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG				WATSON LA
DISCN	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ASPIRIN, CAFFEINE, AND CODEINE PHOSPHATE	A075351	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG				VINTAGE PH
Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Ho

Drug Product List
Therapeutic Equivalence

- Therapeutic Equivalence (TE) codes indicate substitutability between products

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS
RX	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ASPIRIN, CAFFEINE AND CODEINE PHOSPHATE	A203335	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB		
RX	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ASPIRIN, CAFFEINE, AND CODEINE PHOSPHATE	A074951	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB		
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Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS

Drug Product List
Therapeutic Equivalents

- Therapeutic Equivalents:

  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.

Drug Product List
Therapeutic Equivalents

- Pharmaceutically equivalent drug products
  - **Contain**
    - **identical amounts**
    - **identical active ingredient**
    - **identical dosage form**
    - **Identical route of administration**

(81 FR 69638)

Drug Product List
Therapeutic Equivalents

- Bioequivalent
  - the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents becomes available at the site of drug action when administered at the same molar dose under similar conditions

Drug Product List
Therapeutic Equivalence

- Substitutable if "A" rated
  - therapeutically equivalent
  - No known/suspected bioequivalence problem
  - Actual or potential bioequivalence problems resolved with in vivo or in vitro studies to support
- "A" ratings—AB, AA, AN, AO, AP, AT where the second letter provides additional information such as dosage form.
- "AB" – (most common)

Drug Product List: Therapeutic Equivalence

- Not substitutable if “B” rated
  - Not therapeutically equivalent
  - actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence.
- "B" ratings – BX, BC, BE, BN, BP, BR, BS, BT where the second letter provides additional information such as dosage form.
- BX most common

Drug Product List: Therapeutic Equivalence

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS
RX	SUMATRIPTAN SUCCINATE	SUMAVEL DOSEPRO	N022239	INJECTABLE	SUBCUTANEOUS	EQ 4MG BASE/0.5ML (EQ 8MG BASE/ML)	BX	RLD	RS
RX	SUMATRIPTAN SUCCINATE	SUMAVEL DOSEPRO	N022239	INJECTABLE	SUBCUTANEOUS	EQ 6MG BASE/0.5ML (EQ 12MG BASE/ML)	BX	RLD	RS
Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS

Orange Book: Reference Listed Drug (RLD)

- Listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA
  - 21 CFR 314.3(b)

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Ho
RX	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ASPIRIN, CAFFEINE AND CODEINE PHOSPHATE	A203335	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			MAYNE PHA
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Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Ho

Orange Book: Reference Standard (RS)

- Reference Standard-

  The drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval of its ANDA

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Ho
RX	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	BUTALBITAL, ASPIRIN, CAFFEINE AND CODEINE PHOSPHATE	A203335	CAPSULE	ORAL	325MG; 50MG; 40MG; 30MG	AB			MAYNE PHA
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Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Ho

Orange Book: Selecting a RS

- Ordinarily, FDA selects the RLD as the reference standard
- Generally the highest strength available for drug products with approved multiple strengths
- When the innovator RLD is unavailable and there are multiple approved generic products, FDA generally selects the generic market leader as the reference standard

FDA U.S. FOOD & DRUG ADMINISTRATION

PATENTS

Orange Book Patent Listings

NDA applicants are required to submit for listing, patents that protect their approved drug substances, drug product, or approved methods of use

Orange Book Patent Listings

- Patents are required to be submitted on Form **FDA 3542** for Orange Book listing to ensure only specific types of patents are listed

- Types of Patents Listed
  - **Drug Substance (active ingredient)**
  - **Drug Product (formulation/composition)**
  - **Method-of-Use**

- Use of the form can help to ensure complete information is submitted

Orange Book Patent Listings

- **Timely filed Patents**
  - Patent information submitted within 30 days after the date of approval of an NDA or supplement
  - If a patent is issued for a drug substance, drug product, or method of use after an NDA is approved, the applicant must submit to FDA, the required patent information within 30 days of the date of issuance of the patent
  - If the applicant submits required patent information within 30 days, but we notify an applicant that a form is incomplete or that the patent is not eligible for listing, the applicant must submit an acceptable form within 15 days of FDA notification to be considered timely filed

Orange Book Patent Listings

- Patents are listed in the Orange Book per applicant submission - may be challenged by a third party - 21 CFR 314.53(f)(1)
- FDA assumes ***"ministerial"*** role with respect to patent listings
- Disputes resolved in Court - FDA does not act as intermediary/referee

Orange Book: Sample Patent Listing

Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission
7514444	12/28/2026	DS	DP			01/19/2018
8008309	12/28/2026	DS	DP			01/19/2018
8476284	12/28/2026			U-1456 U-1650 U-1946 U-1947		01/19/2018
8497277	12/28/2026			U-1456 U-1491 U-1650 U-1946 U-1947		01/19/2018
8563563	04/26/2027			U-1491 U-1946 U-2219		01/19/2018
8697711	12/28/2026	DS	DP			01/19/2018
8703780	12/28/2026			U-1491		01/19/2018

U.S. FOOD & DRUG ADMINISTRATION

Exclusivity

New Drug Exclusivities

- NCE: for new active ingredients – no 505(b)(2) or ANDA submission for five years; applicants challenging patents can submit at year 4
- Three-year Hatch-Waxman: three-year exclusivity for new condition of approval supported by new, essential clinical studies by applicant– no 505(b)(2) or ANDA approval of new condition for three years
- Orphan: seven-year exclusivity for a product for rare disease indication; blocks against ANDAs and most NDAs
- GAIN: additional five years of exclusivity for products granted a Qualified Infectious Disease Product designation
- Pediatric: six months added to existing patent and exclusivities for conducting pediatric studies

180-Day Exclusivities

- 180-Day Exclusivities (ANDAs only)
  - Patent Challenge (PC): Granted to first applicant to file substantially complete ANDA challenging a listed patent (containing a paragraph IV certification)
  - Competitive Generic Therapy (CGT): Granted to application for drug product with inadequate generic competition, under FDARA

New Drug Exclusivities

Sample of 3-year Hatch-Waxman exclusivity codes

D	NEW DOSING SCHEDULE (SEE INDIVIDUAL REFERENCES)
I	NEW INDICATION (SEE INDIVIDUAL REFERENCES)
M	MISCELLANEOUS EXCLUSIVITY CODES (SEE INDIVIDUAL REFERENCES)
NC	NEW COMBINATION
NDF	NEW DOSAGE FORM
NE	NEW ESTER OR SALT OF AN ACTIVE INGREDIENT
NP	NEW PRODUCT
NP*	NEW PRODUCT (MINT FLAVORED)
NPP	NEW PATIENT POPULATION
NR	NEW ROUTE
NS	NEW STRENGTH

Sample New Drug Exclusivities

Exclusivity Code	Exclusivity Expiration
I-702	01/29/2018
NCE	11/13/2018
I-729	03/04/2019
I-736	05/06/2019
D-165	05/06/2019
I-737	05/06/2019
I-741	01/18/2020
I-753	08/02/2020
ODE-55	11/13/2020
ODE-60	02/12/2021
ODE-72	07/28/2021

In Conclusion

- The Orange Book is a list of drugs approved under Section 505 of the Federal Food, Drug, and Cosmetic Act
- The *Orange Book* is particularly critical in determining when generic drug versions can be substituted for the brand name product.
- Although some outside users repackage the information, the only definitive source for Therapeutic Equivalence (TE) and Reference Listed Drug (RLD) data, as well as Patent and Exclusivity data, is the *Orange Book*.

QUESTIONS

CDER ORANGEBOOK

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