FDA's Orange Book: A Historical Review of 40 Years

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Learning Objectives

At the end of the presentation the participant will be able to:

- Recognize how amendments to the Federal Food Drug & Cosmetic Act (FD&C Act) have shaped the development of the Orange book
- Identify relevant changes to the Orange Book over the past 40 years

Milestones in the Development of the Federal Food, Drug & Cosmetic Act (FD&C Act)

- **1906: Federal Food and Drugs Act**
  - Prohibited misbranding and adulteration of food and drugs
  - No premarket approval of any drugs by FDA. FDA could only take action against a marketed drug if it was found to be adulterated or misbranded
- **1938: Federal Food, Drug, and Cosmetic (FD&C) Act**
  - Required premarket approval of new drugs for ***safety*** before marketing - starting a new system of drug regulation
  - Exempted from the New Drug Application (NDA) process were:
    - Drugs generally recognized as safe (GRAS)
    - Grandfathered Drugs (drugs on the market prior to passage of the Act)
- **1951: Durham-Humphrey Amendment**
  - Separated prescription drugs from Over-the-Counter (OTC) products

Milestones in the Development of the Federal Food, Drug & Cosmetic Act (FD&C Act)

- **1962: Kefauver-Harris Drug Amendments**
  - Required that manufacturers demonstrate ***effectiveness*** of drug products before marketing, as well as safety
  - The new "effectiveness" requirement was retroactive for all NDAs (approximately 3,400) approved only for safety between 1938 and 1962. FDA was mandated to conduct a retrospective evaluation of the effectiveness of these drugs.
    - This major undertaking by the Agency is known by its acronym DESI (Drug Efficacy Study Implementation)
- **1983: Orphan Drug Act**
  - Orphan Drug Exclusivity

Milestones in the Development of the Federal Food, Drug & Cosmetic Act (FD&C Act)

- **1984: Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments)**
  - established the approval pathway for abbreviated new drug applications (ANDA) under section 505(j) of the FD&C Act
  - established provisions for patents and exclusivities related to new drug applications, and 180-day exclusivity for certain ANDA applicants
- **1997: Food and Drug Administration Modernization Act (FDAMA)**
  - repealed 507 (antibiotics)
  - pediatric exclusivity
    - 2002: Best Pharmaceuticals for Children Act (BPCA)
      - reauthorized pediatric exclusivity
- **2003: Medicare Modernization and Prescription Drug Improvement Act (MMA)**
  - Altered key provisions to Hatch-Waxman amendments

Development of the Orange Book: Background and Purpose

- Proposed in 1979 –
  - see notice in the *Federal Register* (44 FR 2932, January 12, 1979)
- 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 for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.

Development of the Orange Book: History and Purpose

General Considerations:

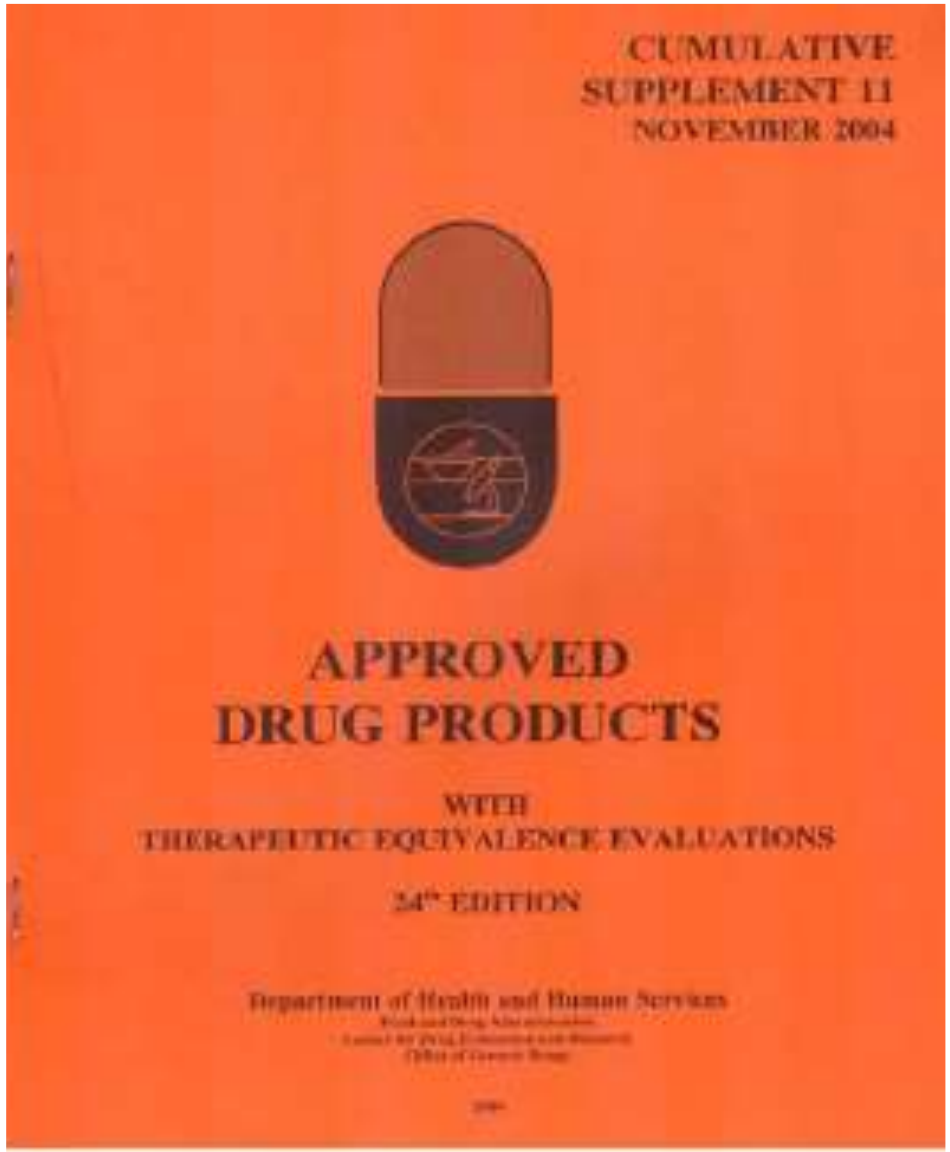
1. Promote public education in the area of DRUG PRODUCT SELECTION
2. Provide information and advice to State and Federal Health Agencies, physicians, pharmacists
3. Foster containment of health care costs

Development of the Orange Book: History and Purpose

Approved Drug Products with Therapeutic Equivalence Evaluations

Finalized October 1980

-45 FR 72582, October 31, 1980



Challenge Question

- Which amendment to the FD&C Act caused the addition of patents to the Orange Book?

A. Durham-Humphrey Amendment

B. Drug Price Competition and Patent Term Restoration Act

C. Kefauver-Harris Drug Amendments

D. Food and Drug Administration Modernization Act

Through the Decades – Significant Updates to the Orange Book

1980 – 1989

Orange Book Development

1990 – 1999

Regulatory Compliance

2000-2009

Technological Advancement

2010-2019

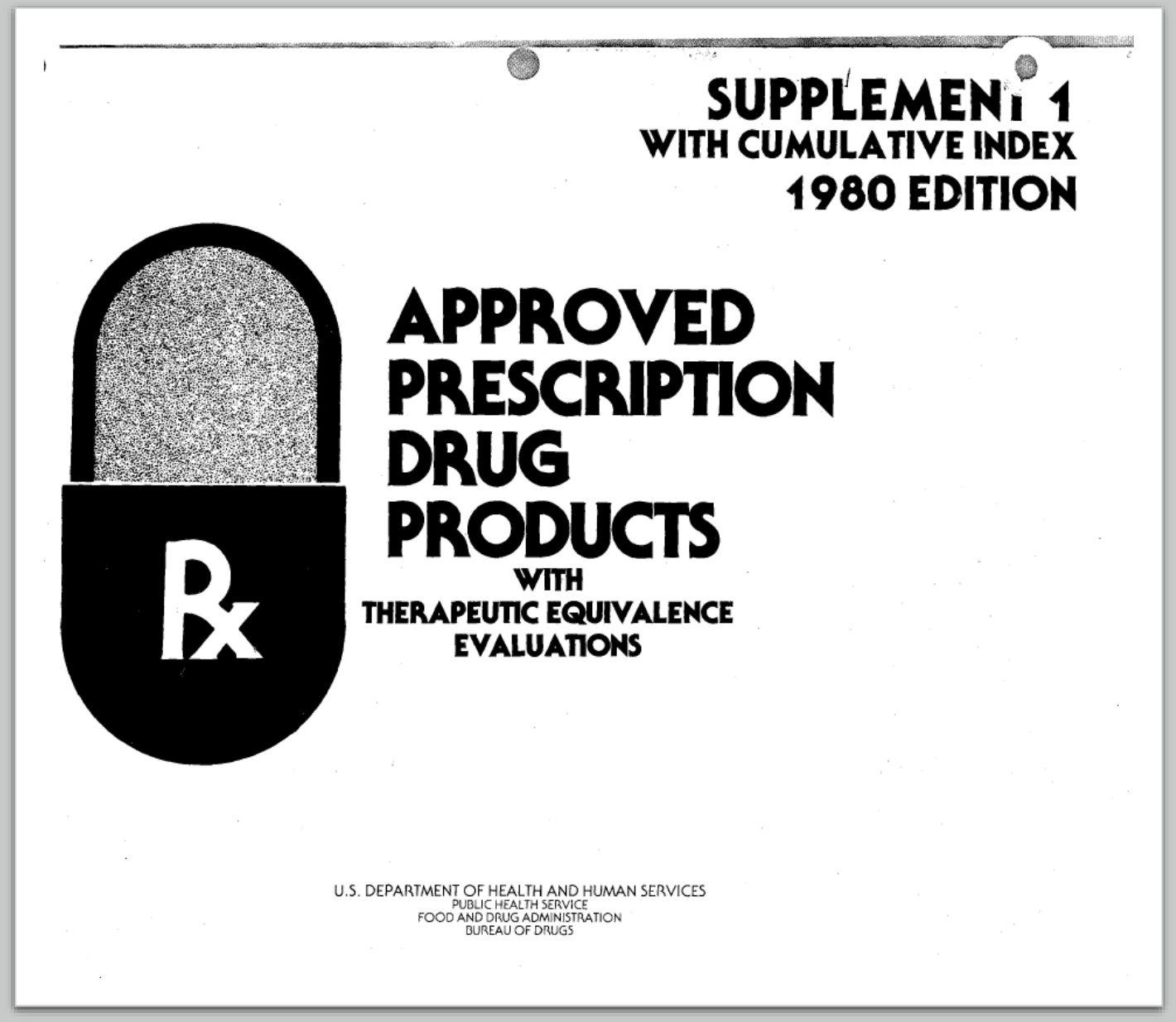
Orange Book Expansion and Transparency

2020+

Orange Book Modernization

1980 – 1989: Orange Book Development

- 1980 – First official Publication of the Orange Book



1980 – 1989: Orange Book Development

- 1984 – Passage of the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman) Amendments
  - 1985 – 6th Edition of the Orange Book Annual Publication
    - FDA began including discontinued drug products in the Orange Book
    - Added to the Orange Book a list of OTC drug products that had been approved in NDAs or ANDAs.
    - Included the 1st Patent and Exclusivity Information Addendum

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1990 – 1999: Regulatory Compliance

- 1992 – FDA issued the final rule for Abbreviated New Drug Applications (ANDAs)
  - Orange Book began identifying the Reference Listed Drug
- 1997 - Pediatric Exclusivity added to the Orange Book in response to the passage of FDAMA
- 1997 – First Orange Book website

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N205551	001	5905082	May 18, 2016	Y	Y		
N205551	001	5905082*PED	Nov 18, 2016				
N205551	001	6294540	May 14, 2018	Y	Y	U - 1572	
N205551	001	6294540*PED	Nov 14, 2018				
N205551	001	6417191	Mar 28, 2016		Y	U - 1572	

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2000-2009: Technological Advancement

- 2003 - FDA started publishing an indicator as to whether a listed patent contains drug substance and/or drug product claims.
- 2005 –
  - FDA made copies of the Orange Book available for download off of the Agency's website.
  - FDA switched from publishing patent listings in a public docket to publishing them daily in the Orange Book.
  - FDA switched from publishing generic drug approvals monthly to publishing them daily

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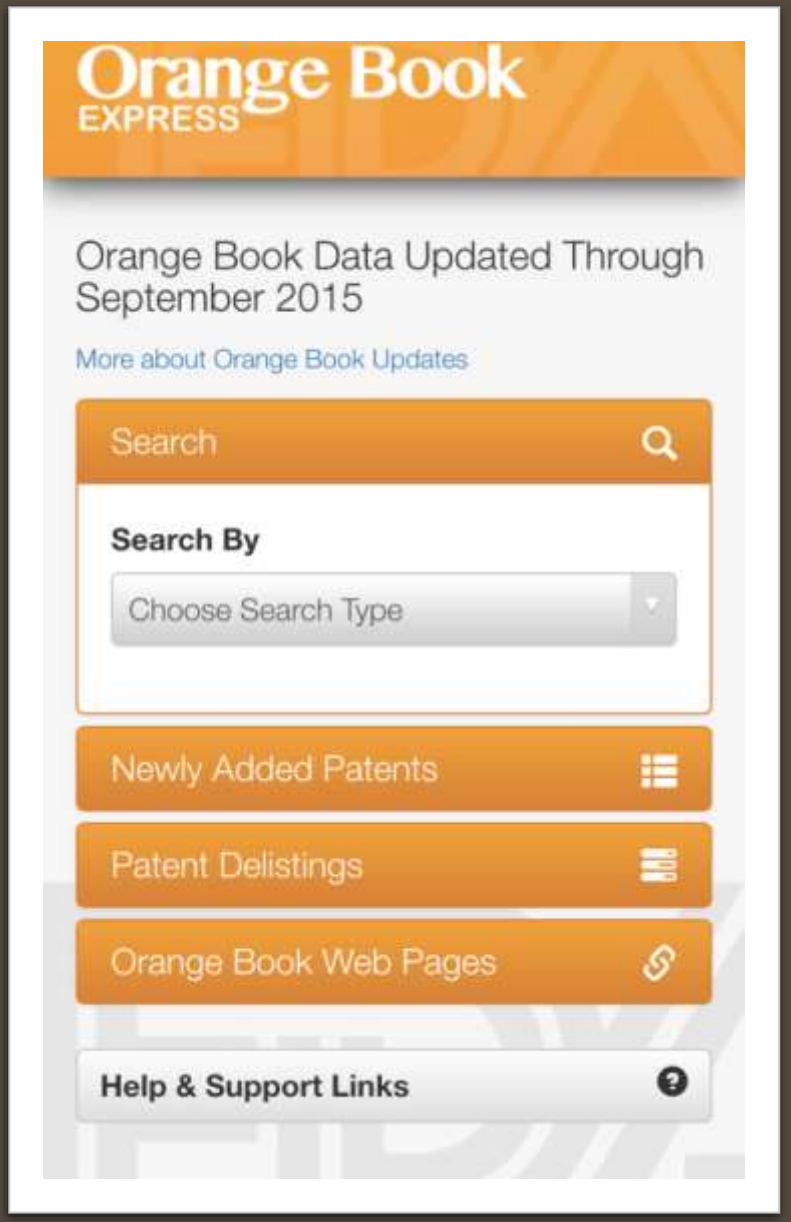
2010-2019: Orange Book Expansion and Transparency

- 2014 – Orange Book staff became a part of the Office of Generic Drug Policy, Division of Legal and Regulatory Support
- 2015 – FDA Releases the “Orange Book Express” App
- 2016 – FDA redesigned the Orange Book website to include commonly used features on the home page and to allow users to better navigate the Orange Book and customize their search.



2010-2019: Orange Book Expansion and Transparency

- 2016 – FDA issued a final rule to implement Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA)
  - 2017 - FDA revised the Orange Book so that drug listings now clarify which listed drugs are RLDs and which are reference standards (see § 314.3(b)), as well as to clarify which products in the "Discontinued Drug Product List" are RLDs.

Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
ABIRATERONE ACETATE	YONSA	N210308	TABLET	ORAL	125MG		RLD	RS	SUN PHARMA GLOBAL FZE
ABIRATERONE ACETATE	ZYTIGA	N202379	TABLET	ORAL	250MG	AB	RLD		JANSSEN BIOTECH INC
ABIRATERONE ACETATE	ZYTIGA	N202379	TABLET	ORAL	500MG		RLD	RS	JANSSEN BIOTECH INC

2010-2019: Orange Book Expansion and Transparency

- 2016 – FDA issued a final rule to implement Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (cont'd)…
  - 2017 - FDA revised the Orange Book to include listed patent submission dates, where available.

Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
7514444	12/28/2026	DS	DP			12/12/2013
8008309	11/13/2027	DS	DP			12/12/2013
8476284	12/28/2026			U-1456 U-1650 U-1946 U-1947		12/12/2013
8497277	12/28/2026			U-1456 U-1491 U-1650 U-1946 U-1947		12/12/2013

2010-2019: Orange Book Expansion and Transparency

- 2016 – FDA issued a final rule to implement Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (cont'd)…
  - 2017 - FDA added the patent listing dispute list to the Orange Book website, which informs stakeholders (1) whether a patent listing dispute has been submitted to FDA and (2) whether the NDA holder has timely responded to the patent listing dispute.
    - https://www.fda.gov/drugs/drug-approvals-and-databases/orange-book-patent-listing-dispute-list
  - 2018 - FDA updated the Orange Book to include descriptions indicating which indication(s) are protected by orphan drug exclusivity.

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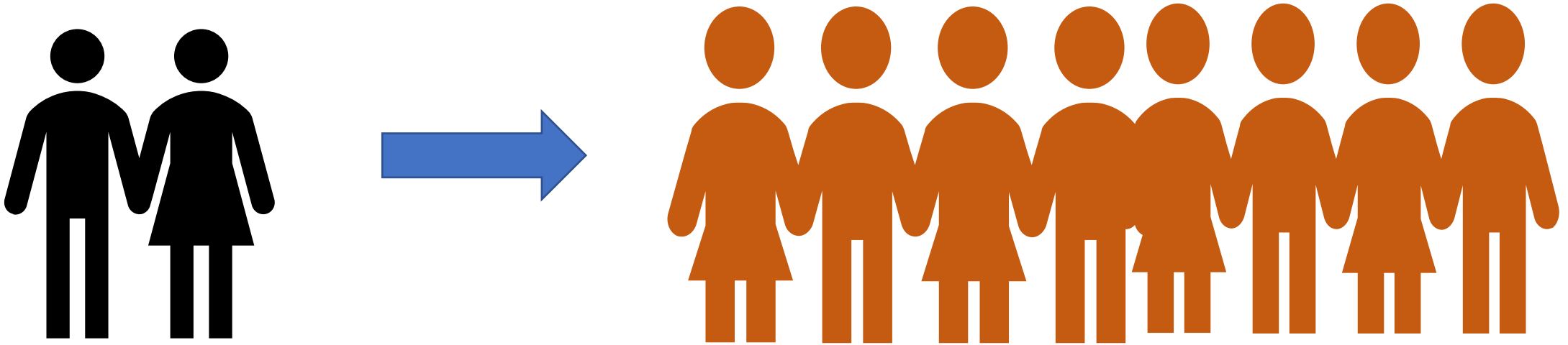
2020 and Beyond: Orange Book Modernization

- 2020 –
  - Publication of the Draft Guidance “Orange Book Questions and Answers”
  - Publication of two public Orange Book focused dockets – Request for Comments
    - Approved Drug Products With Therapeutic Equivalence Evaluations (the “Orange Book”); Establishment of a Public Docket; Request for Comments
    - Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments

Challenge Question

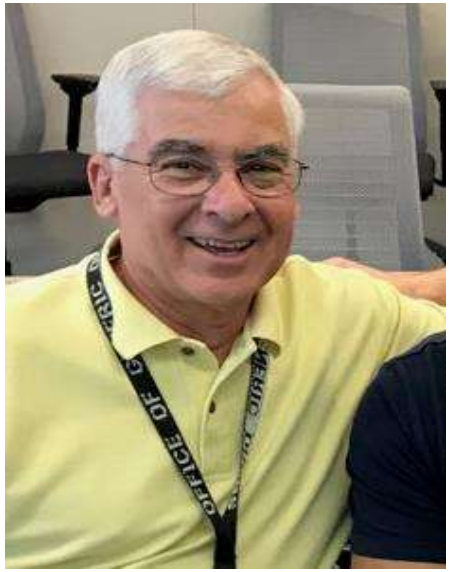
- In what year was the Orange Book modified to clarify which applications were reference standards (RS) versus those that were reference listed drugs (RLDs)?
  A. 1992
  B. 2017
  C. 1994
  D. A. and C.

2020 +: Orange Book Modernization



Orange Book Staff Expansion

Orange Book Long-Term Staff



2020+: Orange Book Modernization

Orange Book Staff 2020

Summary

- Amendments to the FD&C Act have shaped the contents of the Orange Book publication
- Throughout the last 40 years, the FDA has continuously sought to enhance the utilization of the Orange Book and increase the transparency of the information therein
- As part of FDA's Drug Competition Action Plan, we are committed to bringing greater transparency to the generic drug review and approval process, including through any future enhancements to the Orange Book. We will consider the input provided to our recent public dockets as we consider how we may further enhance the Orange Book to optimize its usefulness for our stakeholders and the public.

Looking towards the future….

A vision of Orange Book's future

would not be possible without understanding Orange Book of the past