Orange Book FAQ
Reference Listed Drug and Reference Standard

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Celebrating 40 Years: An In-Depth Examination of the FDA Orange Book
October 28, 2020

Objectives

- Define reference listed drug (RLD) and reference standard (RS)
- RLD and RS FAQ received by the Orange Book Staff

Referencing Approved Drug Products in ANDA Submissions

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Gail Schmerfeld 301-796-9291.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2017
Generics

Differences between RLD and RS

The RLD is the specific listed drug on which the ANDA applicant relies in seeking approval of its ANDA, i.e., the approved drug product the proposed generic drug is intended to duplicate.

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

The Role of an RLD in an ANDA

- The RLD is the listed drug to which the ANDA applicant must show its proposed generic drug is the same with respect to active ingredient(s), dosage form, route of administration, strength, conditions of use, and (with certain permissible exceptions) labeling.

- The ANDA applicant must also demonstrate that the proposed generic drug is bioequivalent to the RLD.

- If the applicant seeks to change its RLD, the applicant must submit a new ANDA.

Reference Standard

- If bioequivalence is not self-evident, there are a variety of methods by which bioequivalence may be demonstrated, including in vivo studies (in human subjects), in vitro studies (conducted in a laboratory), or both.

FDA's Selection of a Reference Standard

- To facilitate generic drug development, FDA generally selects a single reference standard to ensure the greatest level of consistency between a generic drug and its RLD and among generic drugs.

- Where the RLD is marketed, ordinarily it is also the drug product selected by FDA as the reference standard.

- But, where the RLD has been discontinued from marketing for other than safety or effectiveness reasons, FDA may select a different approved drug to serve as the reference standard.

FDA's Selection of a Reference Standard

- In instances in which FDA cannot select the RLD as the reference standard and there are multiple approved generic products to that RLD, FDA usually selects the generic market leader, based on units sold, as the reference standard.

RLD and RS FAQ

- How to identify RLD/RS on Orange Book website and the Portable Document Format, or PDF
- Selection of the RLD
- RS for products with multiple strengths
- RS unavailability

RLD and RS FAQ, continued

- Requesting a new RS or RLD
- Using authorized generic products
- Update occurrence for RLD/RS

Identifying the RLD and RS

- Changes in 2017

- FDA has modified the Orange Book to clarify which drugs are RLDs and which serve as RS.

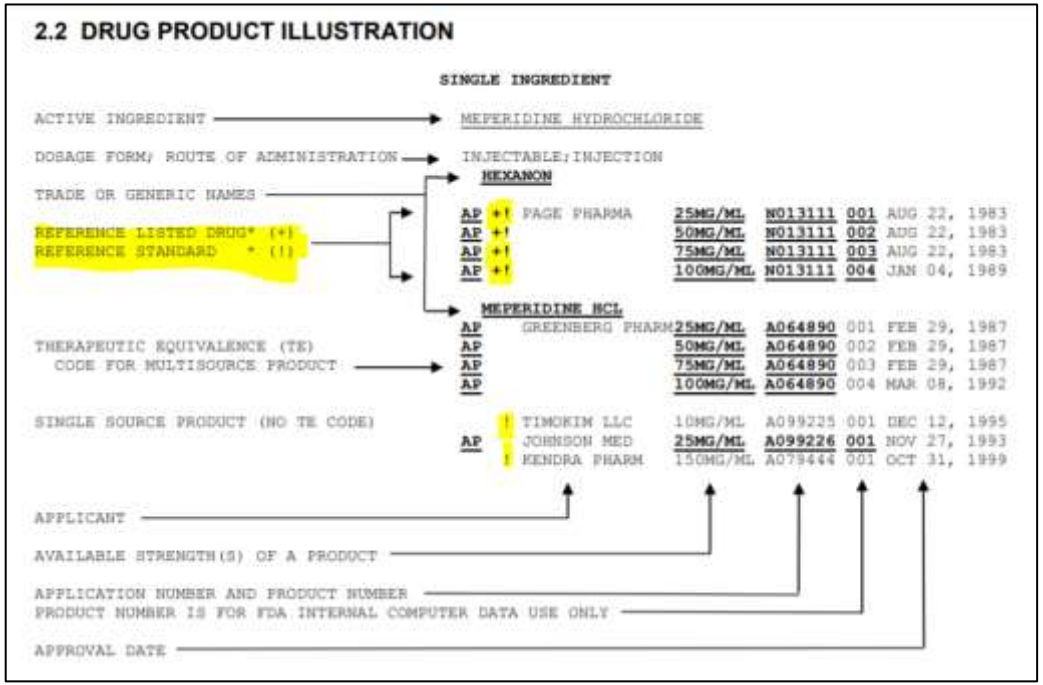
Identifying the RLD and RS

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS
RX	MAGNESIUM SULFATE	MAGNESIUM SULFATE IN DEXTROSE 5% IN PLASTIC CONTAINER	A211965	INJECTABLE	INJECTION	1GM/100ML	AP		
RX	MAGNESIUM SULFATE	MAGNESIUM SULFATE IN DEXTROSE 5% IN PLASTIC CONTAINER	A206486	INJECTABLE	INJECTION	1GM/100ML	AP		
RX	MAGNESIUM SULFATE	MAGNESIUM SULFATE IN DEXTROSE 5% IN PLASTIC CONTAINER	N020488	INJECTABLE	INJECTION	1GM/100ML	AP	RLD	RS
RX	MAGNESIUM SULFATE	MAGNESIUM SULFATE IN DEXTROSE 5% IN PLASTIC CONTAINER	A207349	INJECTABLE	INJECTION	1GM/100ML	AP		
RX	MAGNESIUM SULFATE	MAGNESIUM SULFATE IN DEXTROSE 5% IN PLASTIC CONTAINER	A209932	INJECTABLE	INJECTION	1GM/100ML	AP		

Identifying the RLD and RS

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A209335	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A211682	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A211062	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A212798	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A210611	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A209823	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A209025	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A071655	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A210125	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A074625	TABLET	ORAL	5MG	AB		
RX	OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE	A075079	TABLET	ORAL	5MG	AB		RS

Identifying the RLD and RS



RS for products with multiple strengths

RX	FAMCICLOVIR	FAMCICLOVIR	A201022	TABLET	ORAL	125MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A201333	TABLET	ORAL	125MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A077487	TABLET	ORAL	125MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A091480	TABLET	ORAL	250MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A091114	TABLET	ORAL	250MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A078278	TABLET	ORAL	250MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A202438	TABLET	ORAL	250MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A090128	TABLET	ORAL	250MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A201022	TABLET	ORAL	250MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A201333	TABLET	ORAL	250MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A077487	TABLET	ORAL	250MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A091480	TABLET	ORAL	500MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A091114	TABLET	ORAL	500MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A078278	TABLET	ORAL	500MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A202438	TABLET	ORAL	500MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A090128	TABLET	ORAL	500MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A201022	TABLET	ORAL	500MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A201333	TABLET	ORAL	500MG	AB		
RX	FAMCICLOVIR	FAMCICLOVIR	A077487	TABLET	ORAL	500MG	AB		RS

Additional Resources

- Additions/Deletions for Prescription and OTC Drug Product Lists
- Orange Book Data Files (compressed)
  For more information, including the descriptions of data fields in the Orange Book Search, see Orange Book Data Files.
- Reference Listed Drugs by ANDA Reference Standard List
- Orange Book Patent Listing Dispute List
- BPCIA Orange Book Transition Edition
- Frequently Asked Questions on The Orange Book
- Frequently Asked Questions on Patents and Exclusivity
- Orange Book Preface
- FDA introduces reference standard data updates to the Orange Book

Approved Drug Product List - Orange Book

Reference Listed Drugs by ANDA Reference Standard List

September 2020

DESCRIPTION

This list refers to drug products approved under an Abbreviated New Drug Application (ANDA) that FDA has selected as reference standards and the associated reference listed drugs (RLDs). The purpose of this list is to assist applicants submitting an ANDA to seek approval of a generic drug in identifying an RLD when an ANDA RS has been selected. If the applicant has a question about which listed drug it should refer to as the RLD, the applicant may consult with FDA (refer to section 1.4 Reference Listed Drug and Reference Standard of the Orange Book Preface for more information).

This list is updated monthly. Information in this list is sorted by Active Ingredient(s), Dosage Form, Route, Trade Name, Applicant Name and Strength. Additional information included are marketing status (RX, OTC, DISCN), Application Number, Product Number, and approval date of the Reference Standard.

ACYCLOVIR							
CREAM;TOPICAL							
ACYCLOVIR							
RX	PERRIGO UK FINCO	5%		A208702	001	Feb 04, 2019	RLD: N021478
ACYCLOVIR SODIUM							
INJECTABLE;INJECTION							
ACYCLOVIR SODIUM							
RX	ZYDUS PHARMS	EQ 500MG BASE/VIAL		A206535	001	Aug 31, 2018	RLD: N018603
RX		EQ 1GM BASE/VIAL		A206535	002	Aug 31, 2018	RLD: N018603
ALMOTRIPTAN MALATE							
TABLET;ORAL							
ALMOTRIPTAN MALATE							
RX	AJANTA PHARMA LTD	EQ 12.5MG BASE		A205523	002	Mar 03, 2016	RLD: N021001
AMINOCAPROIC ACID							
TABLET;ORAL							
AMINOCAPROIC ACID							
RX	SUNNY PHARMTECH INC	1GM		A209060	002	Nov 27, 2018	RLD: N015197
AMIODARONE HYDROCHLORIDE							
TABLET;ORAL							
AMIODARONE HYDROCHLORIDE							
RX	UPSHER SMITH LABS	200MG		A075315	001	Dec 23, 1998	RLD: N018972

RLD Designation

- No RLD designated
- Applicants may submit a Controlled Correspondence

GUIDANCE DOCUMENT

Controlled Correspondence Related to Generic Drug Development Draft Guidance for Industry

Draft Guidance for Industry

NOVEMBER 2017

Unavailability of the RS

If the reference standard in the Active Section of the Orange Book (i.e., in the section entitled “Prescription Drug Product List” or “Over-the-Counter Drug Product List”) is not available in the market for a drug product the applicant intends to duplicate, a potential applicant may submit controlled correspondence to FDA asking it to select a reference standard for that drug product.

Authorized Generics in lieu of brand

Authorized generic drug is defined in section 505(t) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and in 21 CFR 314.3(b). A list of currently available authorized generics is available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/fda-listing-authorized-generics.

ANDA applicant may use the authorized generic version of the current reference listed drug as the reference standard for in vivo bioequivalence testing when the brand-labeled version of the reference listed drug is not available.

How often Orange Book is updated

- Changes to RLD and RS are generally reflected in the Orange Book publication once a month
- Monthly updates to Orange Book are made by the end of the following month's second full work week
- https://www.fda.gov/drugs/drug-approvals-and-databases/frequently-asked-questions-orange-book

How often Orange Book is updated

1. **How often is the Orange Book updated?**

Since February 2005, we have been providing daily Electronic Orange Book (EOB) product information for new generic drug approvals. Daily generic updates provide the consumer with the current list of approved generic products which is important for substitution purposes. Previously, a first-time-generic product approved early in the month would not be published in the EOB for several weeks.

The monthly EOB update goal is by the end of the following month's second work week (e.g., November's EOB will be updated by the end of the second full work week in December).

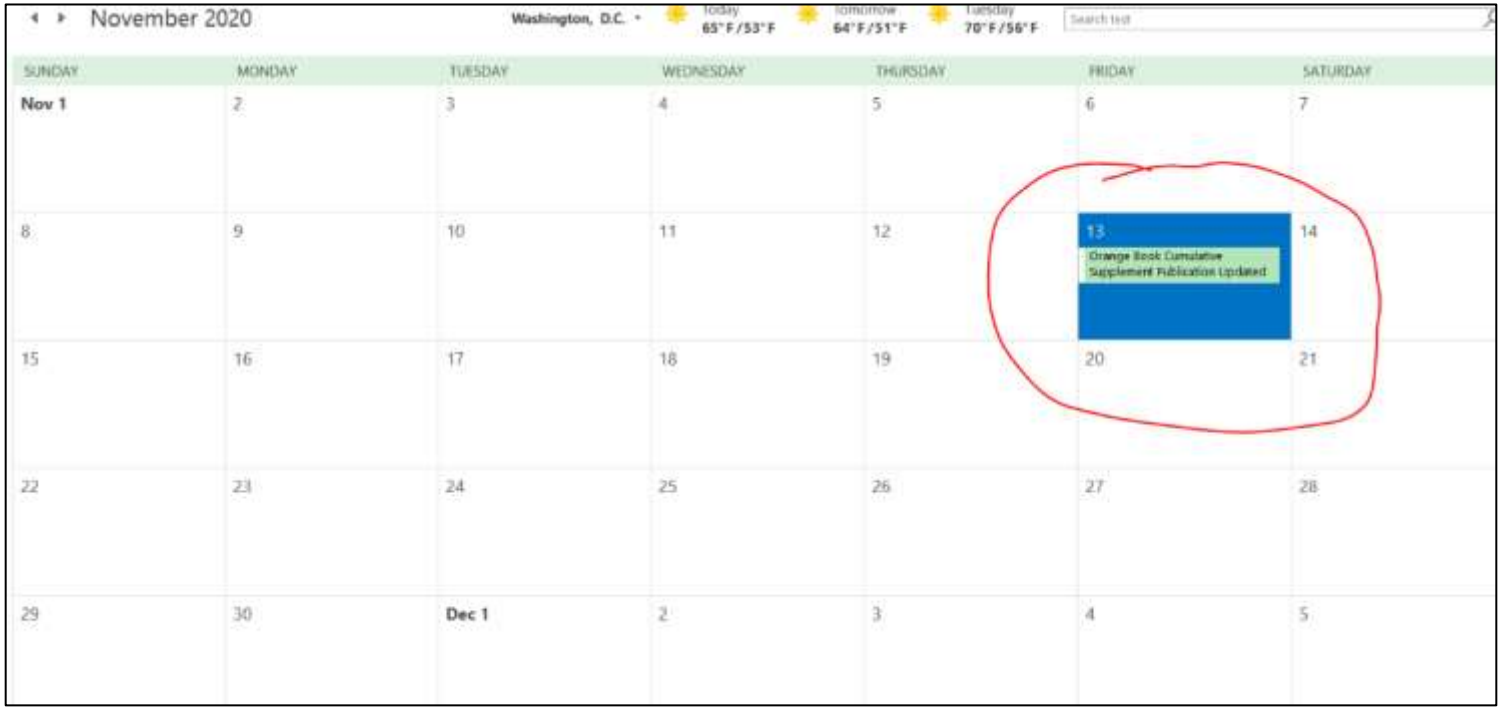
The EOB content includes:

- New Drug Application (NDA) approvals in the EOB month they were approved. NDA application numbers are preceded with "N"
- Abbreviated New Drug Application approvals (ANDA or Generic) as of the date of the daily update. Generic application numbers are preceded with "A".
- All product changes received and processed as of the monthly update date.
- Patent information, also updated daily in the EOB, as of the date of the daily update.
- Exclusivity information updated monthly and current to the date of the monthly EOB update date.

https://www.fda.gov/drugs/drug-approvals-and-databases/frequently-asked-questions-orange-book

How often Orange Book is updated

- October Cumulative Supplement (CS)



Challenge Question #1

In what year did the Orange Book publication first add the reference listed drug (RLD) category?

A) 1980

B) 1984

C) 1992

D) 2017

E) 2019

Challenge Question #2

In what year did the Orange Book publication first add the reference standard (RS) category?

A) 1979

B) 1989

C) 1992

D) 2017

E) 2020

Summary

In this presentation, the following topics were discussed:

- RLD and RS definitions
- RLD and RS categories
- Requesting designation of an RS or RLD
- Authorized Generics
- RLD and RS update timeframe

Questions? Comments?

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