

Case Studies of Using Alternate Reference Standard in Bioequivalence Studies

Xiaojian Jiang, Ph.D.

Division of Bioequivalence II, Office of Bioequivalence
Office of Generic Drugs, CDER/FDA

SBIA Generic Drug Forum – April 10, 2025

Disclaimer

The opinions and information in this presentation are those of this presenter and does not necessarily represent views and/or policies of the U.S. Food and Drug Administration

Topics for Discussion

- Background information
 - Definition of Reference Listed Drug (RLD) and Reference Standard (RS)
 - General Considerations in Selecting RS
- Alternative RS due to the Unavailability or Limited Market Distribution of the Current RS and Other Situations
- Case Studies
- Summary

What is RLD and RS?



- FDA identifies listed drugs in the Orange Book that are eligible to be designated as a Reference Listed Drug (RLD) and/or Reference Standard (RS).
- **RLD** is the listed drug to which the Abbreviated New Drug (ANDA) applicant must show its proposed generic drug is the same with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics.
- **RS** is the specific drug product selected by FDA that the ANDA applicant must use in conducting any in vivo bioequivalence testing required to support approval of its ANDA. FDA also recommends use of the RS for the in vitro testing.

Selection of the RS (1)

- Ordinarily, FDA selects the RLD (highest strength)
- When FDA cannot select the RLD, FDA will generally select a previously approved ANDA, which is therapeutically equivalent to the RLD and is the generic market leader
 - RLD is no longer marketed
 - Prevent a shortage
 - Quantity of the RLD in the distribution is not sufficient for the testing
- Additional factors for selection of the RS
 - Contains all strengths
 - Contains the study strength

Selection of the RS (2)

- Ordinarily, the RS selected by FDA is the RLD.

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	CABOTEGRAVIR SODIUM	VOCABRIA	N212887	TABLET	ORAL	EQ 30MG BASE		RLD	RS	VIIIV HEALTHCARE CO

- RS is the ANDA

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
DISCN	CLARITHROMYCIN	BIAXIN XL	N050775	TABLET, EXTENDED RELEASE	ORAL	500MG **Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons**		RLD		ABBVIE INC

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	CLARITHROMYCIN	CLARITHROMYCIN	A065154	TABLET, EXTENDED RELEASE	ORAL	500MG	AB		RS	DR REDDYS LABORATORIES SA

Selection of the RS (3)

A potential applicant may submit controlled correspondence to ask FDA to select a RS for a drug product when:

- RS was not designated in the Orange Book
- RS is moved to the Discontinued section
- Quantity of the RS in distribution is so limited and not sufficient for the testing
- Potential applicant believes a RS other than the current RS is appropriate

Selection of the RS (4)

If the Agency selects a new RS, that product generally will remain the RS even if the original RS resumes marketing.

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	DOXORUBICIN HYDROCHLORIDE	DOXIL (LIPOSOMAL)	N050718	INJECTABLE, LIPOSOMAL	INJECTION	20MG/10ML (2MG/ML)	AB	RLD		BAXTER HEALTHCARE CORP
RX	DOXORUBICIN HYDROCHLORIDE	DOXIL (LIPOSOMAL)	N050718	INJECTABLE, LIPOSOMAL	INJECTION	50MG/25ML (2MG/ML)	AB	RLD		BAXTER HEALTHCARE CORP
RX	DOXORUBICIN HYDROCHLORIDE	DOXORUBICIN HYDROCHLORIDE (LIPOSOMAL)	A203263	INJECTABLE, LIPOSOMAL	INJECTION	20MG/10ML (2MG/ML)	AB		RS	SUN PHARMACEUTICAL INDUSTRIES LTD
RX	DOXORUBICIN HYDROCHLORIDE	DOXORUBICIN HYDROCHLORIDE (LIPOSOMAL)	A203263	INJECTABLE, LIPOSOMAL	INJECTION	50MG/25ML (2MG/ML)	AB		RS	SUN PHARMACEUTICAL INDUSTRIES LTD

Possible Alternative RS due to Unavailability/Limited Availability



1. Use authorized generic version of the RLD
2. Use other approved ANDA based on the same RLD
3. Use different strength of the RS
4. Use a different dosage form of another RLD or RS for the same route of administration based on publicly available bridging study(ies) conducted by the innovator
5. Use individual component of a fixed-dose combination drug products (FDC) when there was supportive evidence

Possible Alternative RS When Current RS Is Still Available



1. Use other approved ANDA which was previous RS
 - Only if the designated RS is unavailable
 - Procured before discontinuation and unexpired
2. Use RLD instead of currently designated RS
 - Both RLD and RS are on the market
 - Procured the RLD before discontinuation and unexpired

Authorized Generic Drug



1. FDA listing of Authorized Generics (AG)
(<https://www.fda.gov/media/77725/download?attachment>)
2. Same drug product as the RLD under the same NDA
 - Therapeutically equivalent to the RLD
 - May have different color, labeling, packaging, product code/ labeler code (NDC), trade name
 - No brand name in the labeling
 - Marketed by brand or other company with permission
3. NDA holder needs to submit information in the annual report to notify marketing of AG
4. An ANDA applicant may, with proper documentation, use the AG for the BE studies*

Case Studies from Inquiries in the Controlled Correspondences

Case #1: Other Strength(s) of RS



Drug Product: 500 mg and 1000 mg Oral Tablets

RLD/RS: 1000 mg Oral Tablet

Applicant's Query:

- Unable to obtain the RS/RLD, 1000 mg strength due to lack of commercial availability in U.S. market
- Is it acceptable to conduct BE studies using 2 x 500 mg strength of the reference vs 1 x 1000 mg strength of test, and seek waiver for the 500 mg strength of the test product?

FDA's Assessment:

- Confirmed that RS/RLD, 1000 mg strength is not available in the US market
- No approved ANDAs at the time
- The reference, 500 mg strength has been shown to be bioequivalent to the 1000 mg strength in BE studies conducted by the NDA applicant

FDA's Response to the Applicant:

- Proposal to conduct BE studies using 2 x 500 mg reference vs. 1 x 1000 mg test; and request bio-waiver for the test, 500 mg is acceptable

Case#2: Different Dosage Form for the Same Route of Administration



Drug Product: 600 mg Oral Tablets

RLD/RS: RLD discontinued; no new RS designated

Applicant's Query:

- Is it acceptable to conduct BE studies using one 600 mg tablet vs. one capsule of 400 mg ANDA1 and one capsule of 200 mg ANDA2 referred to the same RLD?

FDA's Assessment:

- No approved ANDAs exist for oral tablets
- Under a different NDA, the 400 mg ANDA1 is the designated RS for oral capsule.
- NDA holder is the same for both RLDs (tablet and capsule) and the NDA applicant established BE between them
- Combining two different ANDAs as a RS is not encouraged
- The Agency confirmed that ANDA2 was no longer marketed and moved it to the discontinued section
- No safety concerns were identified for using a higher 1200 mg dose in the in vivo study
- The 200 and 300 mg ANDA1 were approved at the time of assessment and but have not yet been marketed

FDA's Response to the Applicant:

- The applicant proposed approach is not acceptable
- The Agency recommends conducting BE studies using either: 600 mg tablets (T) vs. 2 × 300 mg capsules (R) from ANDA1 if it becomes available, or 2 × 600 mg tablets (T) vs. 3 × 400 mg capsules (R) from ANDA1

Case#3: Different Dosage Form for the Same Route of Administration



Drug Product: Oral Sublingual Tablets

RLD/RS: RLD discontinued; no new RS designated

Applicant's Query:

- provide specific guidance on an appropriate RS

FDA's Assessment:

- No approved ANDAs for oral sublingual tablets
- No Federal Register determination or pending citizen petition regarding reason of withdrawal for the RLD
- BE of Oral Sublingual tablets to other approved dosage form was not established

FDA's Response to the Applicant:

- The Agency is unable to identify an appropriate reference standard at this time

Case#4: Different Dosage Form for the Same Route of Administration



Drug Product: Oral Tablet

RLD/RS: RLD discontinued; no new RS designated

Applicant's Query:

- Is it acceptable to conduct the relative BA study between tablets and oral solution to support BE requirements of an ANDA?

FDA's Assessment:

- No approved oral solution or other dosage forms
- The oral solution manufactured by the applicant is not an FDA-approved drug product.
- No scientific basis to bridge tablets to unapproved oral solution.

FDA's Response to the Applicant:

- The proposed alternate approach is not acceptable
- The Agency is unable to identify an appropriate RS at this time

Case#5: FDC Oral Dosage Form

Drug Product: X1/Y1 Oral Tablets

RLD/RS: RLD discontinued; no new RS designated

Applicant's Query:

- Is it acceptable to conduct BE studies comparing the FDC oral tablet (X1/Y1) to co-administered individual oral tablet (X1 and Y1)?

FDA's Assessment:

- No approved ANDAs for FDC drug product
- No determination whether the RLD was withdrawn from sale for safety or effectiveness
- NDA applicant demonstrated BE between the FDC drug product and co-administered individual components

FDA's Response to the Applicant:

- The proposed alternate approach for demonstrating BE is acceptable
- Submit or refer to a citizen petition seeking a safety and effectiveness determination for the listed drug before or at the same time as any future ANDA submission

Case#6: FDC Oral Dosage Form

Drug Product: X1/Y1 Oral Tablet

RLD/RS: RLD discontinued; no new RS designated

Applicant's Query:

- Is it acceptable to conduct BE studies comparing the X1/Y1 oral tablets to co-administered individual oral tablet (X1 and Y1)

FDA's Assessment:

- No approved ANDAs for FDC drug product
- The NDA applicant did not conduct any study to compare the FDC drug product and co-administered individual components
- The applicant did not provide any information to support the BE

FDA's Response to the Applicant:

- The proposed alternate approach is not acceptable
- The Agency is unable to identify an appropriate reference standard at this time

Summary



- Alternative RS may be used to establish BE and support generic drug approval in some instances
- If the RLD is discontinued, the applicant should submit or reference a citizen petition to determine whether the withdrawal of the RLD from sale was for safety or effectiveness reasons, before or at the time of the ANDA submission
- For any questions on the alternative RS, contact FDA via a controlled correspondence before conducting studies
- The Agency's selection of an alternative RS is based on confirming the unavailability/limited availability of the current RS and relevant scientific considerations

References

- FDA Guidance Document: Referencing Approved Drug Products in ANDA Submissions Guidance for Industry. October 2020
- Paramjeet Kaur. Inquiries About Use of Alternative Reference Standard in Controlled Correspondences: Case Studies. GRx+Biosims 2019.
https://accessiblemeds.org/wp-content/uploads/2024/09/Paramjeet_Kaur_GRxBiosims2019.pdf.
- Authorized Generic CPs: FDA responses to Citizen Petition Docket No. FDA-2014-P-1065, and FDA-2013-P-0040 and FDA-2017-P-5954

Acknowledgements

Paramjeet Kaur, Ph.D. Team Leader

Min Qing, Ph.D. Primary Assessor

Hongling Zhang, Ph.D., Division Director FDA/CDER/OGD/OB/DBII

Bing Li, Ph.D. Associate Director for Science

FDA/CDER/OGD/OB

Office of Generic Drug Policy

The Divisions of Bioequivalence Assessment Teams who assessed these inquires

Thank You