Inquiries About Use of Alternative Reference Standard in Controlled Correspondences: Case Studies

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Disclaimer

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Topics for Discussion

- Background
- Case Studies

Background

- 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 Guidance Document: Referencing Approved Drug Products in ANDA Submissions Guidance for Industry. January 2017

Background

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

- However, where the **RLD** has been **withdrawn** from sale for **reasons other than safety and effectiveness**, FDA may select a previously approved ANDA that referred to the RLD as the RS.

FDA Guidance Document: Referencing Approved Drug Products in ANDA Submissions Guidance for Industry. January 2017

Background

Requesting Selection of a RS

- If there is **no RS designated** in Active Section of the Orange Book for a drug product the applicant intends to duplicate, an applicant may submit **controlled correspondence** requesting the Agency to designate a RS for that drug product.

- If there is a **RS designated** in **Active Section of the Orange Book**, but there are **limited or no quantities in distribution**, or a potential ANDA applicant believes a **RS other than the one selected by FDA is appropriate**, then the potential applicant may **submit a citizen petition under 21 CFR 10.25(a) and 10.30** to FDA to request that it select that different listed drug as a RS.

FDA Guidance Document: Referencing Approved Drug Products in ANDA Submissions Guidance for Industry. January 2017

Case Studies

The following case studies are not generally applicable to all drug products, as responses to inquiries are based on the alignment of certain regulatory requirements and scientific safety considerations that are specific to a particular drug product. If you have a question about what RS to use, we encourage you to contact FDA via a controlled correspondence.

Case Study 1

Drug Product: Oral Solid Dosage Form

Strengths: 5 mg, 25 mg, and 50 mg

RLD and RS: Same i.e., NDA, 50 mg.

Product-Specific Guidance (PSG):

In vivo bioequivalence (BE) studies on the 50 mg strength at a dose of 100 mg. The 5 mg and 25 mg strengths are eligible for waiver of in vivo BE studies under 21 CFR 320.22(d)(2).

Applicant's Query:

- The RS/RLD, 50 mg strength is not available in the US market.
- Is it acceptable to conduct BE study on 25 mg strength by keeping the same dose i.e., 4 x 25 mg test vs. 4 x 25 mg of the reference?.

Case Study 1 (cont.)

FDA's Assessment:

- RS/RLD, 50 mg strength is available in limited quantities.
- FDA can consider selecting a new RS when the Agency determines the quantity of the current RS in distribution is so limited that a potential ANDA applicant is not able to obtain a sufficient quantity for in vivo testing (even if the current RS is not in the Discontinued Section of the Orange Book).[1]
- Numerous approved ANDAs. Selected an approved generic drug as new RS based on:
  - ✓ Market share; and
  - ✓ All 3 strengths are approved under same ANDA.

[1] FDA Guidance Document: Referencing Approved Drug Products in ANDA Submissions Guidance for Industry. January 2017

Case Study 1 (cont.)

FDA's Response to the Applicant:

- A new RS for the 50 mg strength will be listed in the upcoming monthly Orange Book update.

- Please conduct BE studies by comparing the 50 mg strength to new RS, 50 mg per PSG.

Case Study 2

Drug Product: Oral Solid Dosage Form

Strengths: 500 mg and 1000 mg

RLD and RS: Same i.e., NDA, 1000 mg.

PSG: In vivo BE studies on the 1000 mg strength. The 500 mg strength is eligible for waiver of in vivo BE studies under 21 CFR 320.22(d)(2).

Applicant's Query:

- Unable to obtain the RS/RLD, 1000 mg strength due to lack of commercial availability in US 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?

Case Study 2 (cont.)

FDA's Assessment:

- RS/RLD, 1000 mg strength is not available in the US market.
- No approved ANDAs.
- The reference, 500 mg strength has been shown to be bioequivalent to the RS/RLD, 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 Study 3

Drug Product Type: Oral Solid Dosage Form

Strengths: 5 mg, 10 mg, and 20 mg

RLD and RS: Same i.e., NDA, 20 mg.

PSG: In vivo BE studies on the 20 mg strength. The 5 mg and 10 mg strengths are eligible for waiver of in vivo BE studies under 21 CFR 320.22(d)(2).

Case Study 3 (cont.)

Applicant's Query:

- Conducted BE studies on the 10 mg strength (dose: 1 x 10 mg) of the test and reference product under a pending ANDA.
- Unable to procure the RS/RLD, 20 mg strength due to restricted distribution program. Now also unable to procure 5 mg and 10 mg strengths of the RLD.
- Based on BE studies on the 10 mg strength conducted under pending ANDA, is it acceptable to establish BE of the **20 mg strength of the test product by comparing it to 2 x 10 mg strength of the test product**?
- **Alternatively**, is it acceptable to **use foreign-sourced 20 mg strength as RS** for BE testing?

Case Study 3 (cont.)

FDA's Assessment :

- RS/RLD, 20 mg strength is commercially available.
- The test, 10 mg strength is not approved.
- Drug product is not subject to a Risk Evaluation and Mitigation Strategy (REMS).

Case Study 3 (cont.)

FDA's Response to the Applicant (cont.):

- Proposed **test, 10 mg and foreign-sourced, 20 mg strengths** have **not** been **approved under section 505(c) or (j) of the FD&C Act**, and are, therefore, not a listed drug within the statutory meaning.
- The **test, 10 mg must first be approved** under section 505(c) or (j) of the FD&C Act **before any petition** under 21 CFR 10.25(a) and 10.30 seeking designation of this drug product as the RS may be considered.
- Because of the potential for BE inconsistencies that may result from even slight differences between a foreign-approved product and the domestic RLD, it is Agency policy not to accept BE studies based on a foreign-approved product to show that a drug is bioequivalent to the US RLD.

Case Study 3 (cont.)

FDA's Response to the Applicant (cont.):

- Proposed approaches to demonstrate BE are not acceptable.
  - ✓ Use of unapproved 2 x 10 mg test vs. 1 x 20 mg test
  - ✓ Use of foreign-sourced 20 mg strength
- If you are unable to obtain supplies of the drug from the brand company and you believe this refusal constitutes anticompetitive behavior, you can raise the matter with the Federal Trade Commission, which is responsible for addressing anticompetitive behavior.

Case Study 4

Drug Product: Oral Suspension Dosage Form

Strengths: X mg/5 mL

RLD and RS: NDA, X mg/5 mL; RLD discontinued but not for safety or effectiveness; no new RS designated.

Applicant's Query:

- Is it acceptable to use the **X mg tablet dosage** form as the **RS** for any comparative testing required to **demonstrate BE to the Oral Suspension X mg/5 mL** and support filing and approval of an ANDA?
- Alternatively, provide specific guidance on an appropriate RS.

Case Study 4 (cont.)

FDA's Assessment:

- No approved ANDAs for oral suspension dosage form.
- Under a different NDA, tablet dosage form is available in 2 strengths (X mg and Y mg). Y mg strength is listed as the RS.
- NDA holder is same for both tablet and suspension dosage forms. To support the approval of oral suspension dosage, the NDA applicant:
  - ✓ Conducted the bioavailability(BA)/BE studies using the tablet and suspension dosage form.
  - ✓ Established BE between the "Y" mg strength of the tablet dosage form vs. 2 x "X" mg/5 mL dosage form.
- Given that the dose proportionality has been demonstrated over a range, the "X" mg strength of oral suspension was deemed BE to the "X" mg strength of the tablet.
- Per the drug product label, oral suspension may be substituted for oral tablets at the same dosage.

Case Study 4 (cont.)

FDA's Response to the Applicant:

- To support the approval of your ANDA, please conduct BE studies comparing 2 x "X mg"/5 mL strength of your oral suspension dosage form to "Y mg" strength of oral tablet dosage form.

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Thank You