Formulation Considerations for Selecting an Appropriate RLD or RS

Timothy H. Kim, PharmD
Office of Generic Drug Policy (OGDP), Office of Generic Drugs (OGD), Center for Drug Evaluation and Research (CDER), FDA

CRCG QQ Sameness Workshop
December 6, 2022

Objectives

- Provide an overview of formulation considerations for selecting a reference listed drug (RLD) or reference standard (RS) to support development of a generic drug product
  - When an RLD is Discontinued
  - When No RLD or RS is Listed in the Orange Book
  - When RLD Reformulates
  - When There is a Difference in pH Adjuster to the RLD

Inactive Ingredient Sameness

- A drug product intended for parenteral, ophthalmic, or otic use generally must
  - contain the same inactive ingredients
  - in the same concentration
  - as the RLD

21 CFR 314.94(a)(9)(iii-iv)

CONSIDERATIONS FOR SELECTING AN RLD OR RS

RLD is Discontinued

- There may be no RLD available to use for reverse engineering or to test against to establish bioequivalence (BE)
  - Orange Book typically will designate a generic drug of that RLD as an RS
  - RS may be only product available to use for reverse engineering to develop your generic drug product

When an RLD is Discontinued

- Submit a controlled correspondence for Q1/Q2 assessment to the RLD
  - FDA will not provide a Q1/Q2 assessment to an RS
  - Sameness to the RLD is what is required for approval

No RLD or RS is Listed in Orange Book

- Orange Book was updated in January 2017 to clarify which listed drugs are RLDs and which are RSs
  - Resulted in some drug products with no RLD or RS listed in the Orange Book

Designating PANDAs as RLDs

- Pre-Hatch-Waxman ANDAs (PANDAs) were submitted under section 505(b) of the FD&C Act and approved under 505(c) of the FD&C Act for safety and effectiveness

- FDA has determined that PANDAs can be designated as RLDs and has begun designating non-antibiotic PANDAs as RLDs
  - May provide additional possible RLDs to choose from in developing your generic product
  - May improve ability to develop a formulation that meets the requirements

When No RLD or RS is Listed in Orange Book

- Check the list of PANDAs posted on the Orange Book website
- Submit a controlled correspondence to request an RLD or RS designation for your proposed generic drug product

When RLD Reformulates

- RLD may have recently reformulated, but you already developed your drug product against the older version of the RLD

- Consider submitting a waiver request under 21 CFR 314.99(b) (314.99(b) waiver) asking FDA to waive the inactive ingredient requirements at 314.94(a)(9)(iii) or (iv) and permit submission of your generic formulation that is Q1/Q2 same to the older RLD formulation

When There is a Difference in pH Adjuster to the RLD

- The regulations do not expressly identify pH adjusters as ‘‘exception excipients’’ and, as such, the inactive ingredient requirements at 314.94(a)(9)(iii) and (iv) apply to pH adjusters

- Submit a controlled correspondence for a Q1/Q2 assessment of your proposed formulation to the RLD
  - May still be challenging to achieve a Q1/Q2 match for pH adjusters for several reasons, including a lack of quantitative information disclosed on RLD labeling, reverse engineering issues, limited responses from FDA to Q1/Q2 assessment questions

- Applicant may choose to seek approval for a drug product intended for parenteral, ophthalmic, or otic use that contains a Q1 or Q2 difference in pH adjuster to the RLD

When There is a Difference in pH Adjuster to the RLD

- If you believe a non-Q1/Q2 response is due to a difference in pH adjuster, you may consider submitting a 314.99(b) waiver request for the pH adjuster difference in your ANDA

- FDA published draft guidance, *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use* (April 2022)
  - Explains FDA's current thinking on how the role of pH adjusters in a formulation supports the possibility where certain differences in pH adjusters compared to the RLD may be scientifically appropriate and acceptable in an ANDA
  - Provides recommendations on the type of information that applicants should consider submitting with a 314.99(b) waiver request when an ANDA applicant asks the Agency to waive the inactive ingredient requirements for pH adjusters
  - Describes the format and process for submitting such waiver requests

314.99(b) Waiver Requests

- Evaluated on a case-by-case basis within the context of a specific application and the specific waiver request being made during scientific review of the ANDA
- Must be submitted (with supporting documentation) in an ANDA submission
- Must contain at least one of the following:
  1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;
  2) A description of an alternative submission that satisfies the purpose of the requirement; or
  3) Other information justifying a waiver

Effect on Eligibility to Use Certain Approaches to Show BE: 320.22(b)(1)

- Where an applicant seeks a 314.99(b) waiver of inactive ingredient requirements at 314.94(a)(9)(iii) or (iv) for a Q1 or Q2 difference in pH adjuster compared to its RLD, then that ANDA product necessarily does not contain the same inactive ingredients in the same concentration as the RLD for BE to be considered "self-evident" under 21 CFR 320.22(b)(1).

Effect on Eligibility to Use Certain Approaches to Show BE:
Where PSG Recommends Q1/Q2 Sameness for Particular BE Approach

- Product-specific guidance (PSG) may recommend that an ANDA product be Q1/Q2 the same as its RLD to use a particular approach recommended in the PSG to demonstrate BE.

PSG Recommendation

Recommended Study: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product all of the following criteria should be met:

i. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same[3].

Example Drug Products (list not comprehensive)

Cyclosporine Ophthalmic Emulsion
Prednisolone Acetate Ophthalmic Suspension/Drop
Loteprednol Etabonate Ophthalmic Gel
Timolol Maleate Ophthalmic Solution/Drops
Propofol Injection

Effect on Eligibility to Use Certain Approaches to Show BE:
Where PSG Recommends Q1/Q2 Sameness for Particular BE Approach

- Recommendations in a PSG are not binding, and applicants may use an alternative approach if it satisfies the statutory and regulatory requirements.

- Scientific principles that provide support for a waiver of the inactive ingredient requirements under 314.94(a)(9)(iii) and (iv) for a difference in pH adjuster may, in some cases, also provide support for an applicant's scientific justification for use of a particular BE approach.

Requesting Waiver of Evidence of in vivo BE

- Waiver under 314.99(b) ≠ waiver under 21 CFR Part 320 (e.g., 320.22)
  - 314.99(b) waiver request permits an applicant to seek waiver of requirements under 314.92 through 314.99, including the inactive ingredient requirements at 314.94(a)(9)(iii) and (iv) (i.e., Q1/Q2 difference in pH adjuster of a parenteral, ophthalmic or otic drug).
  - The requirements for BE are governed by the regulations set forth in 21 CFR Part 320. Thus, a waiver of evidence of in vivo BE (e.g., 320.22(b)(1)) is different from a waiver under 314.99(b), and a waiver under 314.99(b) does not also waive the requirement to submit evidence of in vivo BE.

- We encourage an applicant who plans to submit a waiver request under 314.99(b) for a difference in pH adjuster and use an in vitro approach to establish BE to contact the Agency to discuss the particular approach to establish BE for that drug product.


FDA
U.S. FOOD & DRUG
ADMINISTRATION