Q1/Q2 Assessment and Regulatory Pathway for Biowaiver of Injectable Solutions

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 3: Simple Injectables

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- Describe the Code of Federal Regulations Related to Biowaivers for Injectable Solutions
- Learn assessment using appropriate regulation through case study
  - Considerations for differences in exception excipients
  - Considerations for differences in non-exception excipients
  - Considerations for different dosage forms and different strengths
  - Considerations for multiple administration routes

Code of Federal Regulations

Code of Federal Regulations Title 21 Section 320.22

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

1) *The drug product:*

   i. ***Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and***

   ii. ***Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.***

Code of Federal Regulations Title 21 Section 314.94

Inactive ingredient changes permitted in drug products intended for parenteral use. Generally, a drug product intended for parenteral use must contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. ***However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.***

Code of Federal Regulations Title 21 Section 314.99

(b) ***An applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant must comply with the requirements for a waiver under § 314.90****. If FDA grants the applicant's waiver request with respect to a requirement under §§ 314.92 through 314.99, the waived requirement will not constitute a basis for refusal to approve an ANDA under § 314.127.*

Case Studies

Case #1: Q1/Q2 Assessment for Exception Excipients

Proposed test formulation is not Q1/Q2 to the reference listed drug (RLD) in exception excipients

	RLD	Proposed Test
Inactive Ingredient - 1	A	A
Inactive Ingredient - 2	B	B
Buffer	Sodium Citrate	Mannitol
Antioxidant	Sodium Sulfite	-

Q1/Q2 Assessment Consideration:

- Per 21 CFR 314.94(a)(9)(iii), a variation between test and RLD products is allowed for parenteral formulations with respect to **buffer, preservative, and antioxidant** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the **differences do not affect the safety or efficacy of the proposed drug product**.
- The buffer, preservative, and antioxidant amount should be below the levels in FDA-approved drug products for the same route of administration and context of use.
- Differences on exception excipients in case #1 are acceptable under 21 CFR 314.94(a)(9)(iii).

Case #2: Q1/Q2 Assessment with RLD Formulation Change

RLD formulation was changed (non-exception excipient); proposed test formulation is Q1/Q2 to the original RLD formulation

	Original RLD	Current RLD	Proposed Test
Inactive Ingredient - 1	A	A	A
Inactive Ingredient - 2	B	B	B
Tartaric acid (non-exception excipient)	-	2.25 mg/mL	-
Disodium edetate, Dihydrate (non-exception excipient)	-	0.20 mg/mL	-

Q1/Q2 Assessment Consideration:

- A 314.99(b) waiver is appropriate only when the RLD formulation change is not for safety or effectiveness reasons.
- Bio-waiver is granted under 21 CFR 314.99(b) for case #2.

Case #3: Q1/Q2 Assessment when RLD and RS are Different

Proposed test formulation is not Q1/Q2 to the RLD (non-exception excipients); but Q1/Q2 to RS

	RLD	RS	Proposed Test
Inactive Ingredient - 1	A	A	A
Inactive Ingredient - 2	B	B	B
Isotonic Agent	Sodium Chloride	Sodium Citrate	Sodium Citrate

Q1/Q2 Assessment Consideration:

- A 314.99(b) waiver maybe considered with supporting documentation for the request.
- The acceptability of a request for waiver under 21 CFR 314.99(b) will be determined during the scientific review of the ANDA.

Case #4: Q1/Q2 Assessment for Dosage Form Change

Proposed test formulation is Q1/Q2 to RLD formulation with different dosage forms

	RLD (Solution for Injection)	Proposed Test (Powder for Injection)
Inactive Ingredient - 1	A	A
Inactive Ingredient - 2	B	B
Inactive Ingredient - 3	C	C

Q1/Q2 Assessment Consideration:

- Per 21 CFR 314.93, an approved Suitability Petition is required for changing the dosage form prior to ANDA submission.

Case #5: Q1/Q2 Assessment for Strength Change

Proposed test formulation is Q1/Q2 to RLD formulation with different strengths

	RLD (X mg/mL)	Proposed Test (Y mg/mL)
Inactive Ingredient - 1	A	A
Inactive Ingredient - 2	B	B
Inactive Ingredient - 3	C	C

Q1/Q2 Assessment Consideration:

- A Suitability Petition requesting the change in strength must be approved prior to submitting an ANDA
- A 314.99(b) waiver maybe considered.

Case #6: Q1/Q2 Assessment for Multiple Administration Routes

Proposed test formulation is Q1/Q2 to RLD formulation with multiple administration routes

	RLD	Proposed Test
Administration Routes	Intravenous; intramuscular; subcutaneous; endotracheal	Intravenous; intramuscular; subcutaneous; endotracheal
Inactive Ingredient - 1	A	A
Inactive Ingredient - 2	B	B
Inactive Ingredient - 3	C	C

Q1/Q2 Assessment Consideration:

In vivo BE study requirements for the intravenous, intramuscular and subcutaneous routes of administration may be waived under 21 CFR 320.22(b)(1) and for the endotracheal route of administration, FDA can evaluate BE using in vitro approaches under 21 CFR 320.24(b)(6).

Case #7: Q1/Q2 Assessment for Special Administration Route

Proposed test formulation is Q1/Q2 to RLD formulation as cardiac perfusion

	RLD	Proposed Test
Administration Routes	Cardiac Perfusion	Cardiac Perfusion
Inactive Ingredient - 1	A	A
Inactive Ingredient - 2	B	B
Inactive Ingredient - 3	C	C

Q1/Q2 Assessment Consideration:

21 CFR 320.22(b)(1) can be utilized as cardiac perfusion can be considered parenteral solution for infusion.

Challenge Question #1

Differences between the proposed test and RLD formulations for exception excipients in a parenteral drug product may be acceptable under:

A. 21 CFR 314.99 (b)

B. 21 CFR 320.24 (b)(6)

C. 21 CFR 314.94(a)(9)(iii)

Challenge Question #2

Which of the following statements is NOT true?

A. As long as the proposed test formulation is Q1/Q2 the same to the original RLD formulation, waiver request can be granted per 314.99(b)

B. 314.99(b) wavier may be granted when test formulation is different from the RLD formulation in non-exception excipients

C. Drug product with multiple administration routes can be evaluated for BE under different regulatory provisions

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