Navigating Formulation Assessment: Considerations When Preparing the Q1/Q2 Sameness Inquiry

Qiangnan Zhang, Ph.D.
Staff Fellow
Division of Therapeutic Performance I, Office of Generic Drug
CDER | US FDA

Navigating Controlled Correspondences to
Support Generic Drug Development
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Outline

- Definition Q1 (Qualitative)/Q2 (Quantitative) sameness
- When the Q1/Q2 sameness is involved in generic product development
- Best practices for preparation of a Q1/Q2 Controlled Correspondence (CC)
- Different types of FDA responses related to Q1/Q2 sameness CC

What is Q1/Q2 Sameness?

- Q1 sameness means that the test product uses the same inactive ingredient(s) as the reference listed drug (RLD) product
- Q2 sameness means concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product

When Q1/Q2 involved in generic development?

- 21 CFR 314.94 (a)(9)
  - (iii) Inactive ingredient requirements 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.

  - (iv) inactive ingredient requirements in drug products intended for ophthalmic or otic use

    Generally, a drug product intended for ophthalmic or otic 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, substance to adjust tonicity, or thickening agent** 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, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions of irritability.

When Q1/Q2 involved in generic development? (Cont'd)

- For products other than for parenteral, ophthalmic, or otic use, PSGs sometimes recommend specific BE approaches that may be suitable when formulation is Q1/Q2 to the RLD

Active Ingredient:	Doxycycline hyclate
Dosage Form; Route:	System, extended release; periodontal
Recommended Studies:	Two options: (1) One in vitro drug release study with supportive characterization studies or (2) one in vivo bioequivalence study with clinical endpoints

I. Option 1: One in vitro drug release study with supportive characterization studies

To qualify for the in vitro studies recommended in this guidance, all of the following criteria should be met:

1. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).

PSG on doxycycline hyclate periodontal product

How Q1/Q2 sameness is assessed?

- Q1: Chemical identity of an inactive ingredient
  - Clear information on name, grade, salt form
  - Comparative characterization data may be required (e.g., LG polymers)
- Q2: Quantity of an inactive ingredient
  - Percent difference (%) of an inactive ingredient in the Test (T) and Reference (R) product (i.e., (T-R)/R*100 is within ±5%)

Preparation of Q1/Q2 CC

An example composition table

- A Q1Q2 CC can contain up to 3 test formulations for assessment
- Each test formulation should have a well-presented composition table* as shown below

Component	**Function**	Quantity		
		% (w/v)	% (w/w)	mg/mL
Active ingredient		31.50	30.00	315.00
Edetate Disodium Dihydrate (USP)	Preservative	2.10	2.00	21.00
Acetic Acid (USP)	Buffer	1.31	1.25	13.13
Polysorbate 80 (USP)	Suspending agent	2.31	2.20	23.10
Povidone K17 (USP)	Stabilizer	2.42	2.30	24.15
Water for injection (USP)	Solvent	q.s	q.s to 100	q.s
Nitrogen	Processing aid	-	-	-

*Hypothetical data for illustrative purpose

Specific gravity: 1.05 g/mL

An example composition table Cont'd

Component	Function	Quantity		
		% (w/v)	% (w/w)	mg/mL
Active ingredient		31.50	30.00	315.00
Edetate Disodium Dihydrate (USP)	Preservative	2.10	2.00	21.00
Acetic Acid (USP)	Buf			
Polysorbate 80 (USP)	Sus age			
Povidone K17 (USP)	Sta			
Water for injection (USP)	Sol			
Nitrogen	Processing aid			

Official USP-NF monograph title or the Global Substance Registration System (GSRS) preferred name

USP-NF title may refer to a family or product line; the inactive ingredient grade should be clearly specified

Specific gravity: 1.05 g/mL

An example composition table Cont'd

Component	Function	Quantity		
		% (w/v)	% (w/w)	mg/mL
Drug A	Active ingredient	31.50	30.00	315.00
Edetate Disodium Dihydrate (USP)	Preservative	2.10		
Acetic Acid (USP)	Buffer	1.31		
Polysorbate 80 (USP)	Suspending agent	2.31		
Povidone K17 (USP)	Stabilizer	2.42		
Water for injection (USP)	Solvent	q.s		
Nitrogen	Processing aid			

If it is intended to have certain difference in test formulation with regard to permissible excipients, it is recommended that the function of the excipient is accurately identified.

Processing aids are not within the scope of Q1/Q2 assessment and should be clearly labeled if included in the test formulation.

An example composition table Cont'd

Component	Function	Quantity		
		% (w/v)	% (w/w)	mg/mL
Drug A	Active ingredient	31.50	30.00	315.00
Edetate Disodium Dihydrate (USP)	Preservative			
Acetic Acid (USP)	Buffer			
	Suspending agent			
	Stabilizer			
	Solvent	q.s	q.s to 100	q.s
Nitrogen	Processing aid		-	-

Hydration form should be clearly identified for proper Q2 assessment

Applicants should list nominal amounts of inactive ingredients in composition statements; overage is not within the scope of Q2 assessment

Specific gravity 1.05 g/mL

An example composition table Cont'd

Component	Function	Quantity		
		% (w/v)	% (w/w)	mg/mL
Drug A	Active ingredient	31.50	30.00	315.00
Edetate Disodium Dihydrate (USP)	Preservative	2.10	2.00	21.00
Acetic Acid (USP)	Buffer	1.31	1.25	13.13
Polysorbate 80 (USP)	Suspending agent	2.31	2.20	23.10
Povidone K17 (USP)	Stabilizer	2.42	2.30	24.15
	Solvent	q.s	q.s to 100	q.s
	Processing aid		-	

Specific gravity: 1.05 g/mL

Units of measure for the quantity or concentration of inactive ingredients should be clearly listed (e.g., weight per weight (w/w)%, weight per volume (w/v) %)

For ingredients that may be added based on a volume basis, include calculation/equivalent amount for ingredients

Percentage for w/w should total 100% while w/v may exceed 100% for suspension products depending on the density of the product.

When comparative characterization data to support Q1 sameness

- Comparative characterization data on finished product to support the Q1 sameness of the excipient
  - Starting materials do not represent the component in the finished product (cross-linked elastomer)

    Poly (dimethylsiloxane) elastomer (PDMS)
  - When an excipient may be altered during manufacturing

    LG Polymers: poly lactic-co-glycolic acid/poly lactic polymer (PLGA/PLA)

LG polymer

- LG Polymers: Poly lactic-co-glycolic acid/poly lactic polymer (PLGA/PLA)
- Comparative physicochemical data on polymer extracted from **finished test product and RLD** including polymer composition (molar ratio between glycolide and lactide), molecular weight and weight distribution, and polymer architecture (e.g., linear or branched) should be provided. Branch frequency should be provided if it is a branched polymer.

Table 1. The L:G ratio of the PLGA polymer determined by 1H NMR*

Sample	%(mol) of lactide	%(mol) of glycolide
Test product	75	25
RLD	75	25

Table 2. Molecular weights measured by GPC*

Sample	Mw	Mn	Mw/Mn
Test product	83000	49500	1.68
RLD	82000	49000	1.67

*Hypothetical data for illustrative purpose

LG polymer

- Characterization on polymer mixture without separation of individual PLGA components*
- PLGA characterization literature for reference:
  - Hardar J, et al., Characterization of branched poly(lactide-co-glycolide) polymers used in injectable, long-acting formulations. Journal of Controlled Release, 2019, 304: 75-89
  - Garner J, et al. A protocol for assay of poly(lactide-co-glycolide) in clinical products. International Journal of Pharmaceutics, 2015, 495(1): 87-92
- In addition, to support quality assessment of the test product, provide characterization on the extracted PLGA including, but not limited to polymer end cap analysis, inherent viscosity, and glass transition temperature

* Draft Guidance on Risperidone PSG_212849

Special consideration: difference in pH adjuster

- In general, for products for parenteral, ophthalmic, or otic use, any difference other than a difference in an exception excipient per 314.94(a)(9)(iii) and (iv) will lead to Refuse to Receive (RTR) of the ANDA
- OGD draft guidance, *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use* (April 2022), provides potential pathway for applicants to file an ANDA with difference in pH adjuster
- A test formulation that differs in pH adjuster and without waiver request for pH adjuster difference is likely to be RTR; it is recommended applicants submit a CC to seek FDA's feedback on your proposed justification for a pH adjuster difference in support of your planned 314.99(b) waiver request.
- Final acceptability of pH adjuster waiver is an ANDA assessment issue

FDA responses to Q1/Q2 Sameness

Formulation is Q1/Q2 same as the RLD

- With respect to [formulation X], OGD has made a preliminary determination that it would not likely refuse to receive an ANDA submitted pursuant to section 505(j)…
- If the product is a parenteral solution:
  - With respect to [formulation X],OGD would likely grant a waiver of in vivo bioequivalence because BE would be self-evident pursuant to 21 CFR 320.22(b)(1)
- If the product is not for parenteral/ophthalmic/otic use and the sameness is recommended by PSG,
  - With respect to [formulation X], OGD would likely recommend the studies described in PSG to establish BE.

Different to exception excipient

- With respect to [formulation X], OGD has made a preliminary determination that it would not likely refuse to receive an ANDA submitted pursuant to section 505(j)…
- OGD would not likely grant a waiver of in vivo bioequivalence because bioequivalence would not be self-evident… Your proposed formulation is not Q1/Q2 the same as the RLD with respect to one or more inactive ingredients.
- OGD would likely recommend:
  - If PSG available: the following approach to establish bioequivalence: [Option 1, Option 2] described in PSG.
  - If no PSG: an appropriate in vivo BE study or studies to establish bioequivalence with respect to your proposed generic formulations.

Q1/Q2 different than RLD

- OGD has made a preliminary determination that it would likely refuse to receive an ANDA based on [formulation X]… Your proposed formulation is not Q1/Q2 the same as the RLD with respect to one or more inactive ingredients.

Useful resources

- 21 CFR 314.94(a)(9)(iii) and (iv)
- Guidance for Industry
  - *Controlled Correspondence Related to Generic Drug Development* (March 2024)
  - *Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs* (April 2024)
  - *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use* (April 2022)
- Latest RLD drug product labeling: **https://www.accessdata.fda.gov/scripts/cder/daf/**
- GDUFA research outcomes

Conclusion

- Q1/Q2 sameness refers to the same inactive ingredients (identity) and amounts (each within ±5%) to the RLD.
- The provided test product composition table should have clear identification of inactive ingredients and accurately list the amount for each inactive ingredient.
- To support Q1 sameness of LG polymer, comparative characterization data on the LG polymer extracted from finished product should be provided.
- It is recommended applicants submit a CC to seek FDA's feedback on your proposed justification for a pH adjuster difference in support of your planned 314.99(b) waiver request. Whether the potential waiver request for differences of pH adjuster can be granted is an ANDA assessment issue.

Questions?

Qiangnan Zhang, Ph.D.
Staff Fellow, US Public Health Service
Division of Therapeutic Performance I, Office of Generic Drug
CDER | US FDA

[qiangnan.zhang@fda.hhs.gov]


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