FDA Responses to Questions on Q1/Q2 Sameness

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Excipients and Formulation Assessments of Complex Generic Products:
Best Practices and Lessons Learned
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Objectives

- Provide an overview of FDA's obligations to maintain confidentiality of trade secret information

- Clarify the different types of FDA responses related to Q1/Q2 sameness
  - When drug product is required to be Q1/Q2 same
  - When PSG recommends a drug product to be Q1/Q2 same

FDA Responses

- Generally focused on providing feedback to assist applicants in meeting requirements for approval of their application
- Limited by FDA's obligations to protect the disclosure of trade secret information

Trade Secret Information

- FDA defines as “any commercially valuable plan, **formula**, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort.” - 21 C.F.R. § 20.61(a)

Labeling Requirement

- Generally requires the name of all inactive ingredients to be included on the labeling of drug products intended for parenteral, ophthalmic, and otic use
- Parenteral drugs are also required to disclose the quantitative amount of the ingredients, except for pH adjusters and tonicity agents, but water does not need to be named

- 21 CFR 201.100(b)(5)

How FDA Responds

- Depends on:
  - Whether the drug product is required to be Q1/Q2 same as the RLD,
  - What information is publicly available for the drug product in question, and
  - How the question is asked

RESPONSES WHEN DRUG PRODUCT REQUIRED TO BE Q1/Q2 SAME

When does FDA respond directly to Q1/Q2 sameness questions?

- When the drug product is required by regulation to be Q1/Q2 same as the RLD pursuant to 21 CFR 314.94(a)(9)(iii) and (iv)
  - Drugs intended for parenteral, ophthalmic, or otic use

- PSG is not necessary to receive a response on QQ assessments.

Q1/Q2 Assessment Responses

- **Where 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 a solution:* With respect to [formulation X],OGD would likely grant a waiver of in vivo bioequivalence because bioequivalence would be self-evident pursuant to 21 CFR 320.22(b)(1)

Q1/Q2 Assessment Responses

- **Where formulation is different with respect to exception excipient(s):**
  - 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 establishing 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 Assessment Responses

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

Q1/Q2 Assessment Responses

- Ultimately, whether OGD will receive an ANDA for substantive review will be determined during the filing review of the submitted ANDA.
- The approvability of your product will be determined during the scientific review of your ANDA.
- Inactive ingredient quantity or concentration (Q2) in your formulation should be justified.
  - For ANDA receipt, applicants may justify excipient levels by referencing the applicable current Inactive Ingredient Database (IID) listing or by submitting an adequate justification supporting the safety of the excipient at the proposed level.

Why is FDA referring me to the IID?

- Section 505(j)(4)(H) of the Federal Food, Drug & Cosmetic Act requires inactive ingredient to be safe for use.
- While the amount of an inactive ingredient in the proposed formulation *may* be Q2 same as the RLD (i.e., within 5% of the amount used in the RLD), the amount used in the proposed formulation may still pose safety concerns because it exceeds the max listed in the IID.

	RLD	Test	Q2?	Safety Check Needed?
Ingredient X	5mg	5.24mg	Yes (+4.8%)	
IID Max	5mg	5mg		Yes, Exceeds IID Max

RESPONSES WHEN PSG RECOMMENDS A DRUG PRODUCT TO BE Q1/Q2 SAME

Why isn't FDA saying my formulation is or is not Q1/Q2 the same? Why is a BE approach referenced?

- If the drug is not a parenteral, ophthalmic, or otic product but PSG criteria calls for Q1/Q2 sameness, the Q1/Q2 sameness is not a requirement for approvability of an ANDA, and as such FDA does not comment on formulation sameness in such instances
  - Generally, an ANDA applicant may include different inactive ingredients for a drug that is not a parenteral, ophthalmic, or otic product provided that the differences are identified and characterized with information demonstrating they do not affect the safety or efficacy of the drug product.

- Instead, FDA will provide a response on the acceptability of a BE approach based on the proposed formulation

Why isn't FDA saying my formulation is or is not Q1/Q2 the same? Why is a BE approach referenced?

- If asking about whether a drug that is not a parenteral, ophthalmic, or otic product is Q1/Q2 same as the RLD, FDA will decline to provide a response

- If asking about whether a formulation is Q1/Q2 same as the RLD to use an in vitro approach or waiver option described in a PSG for a drug that is not a parenteral, ophthalmic, or otic product, FDA will provide preliminary feedback on the acceptability of the proposed BE approach based on the proposed formulation submitted
  - Must use "the most accurate, sensitive, and reproducible approach" pursuant to 21 CFR 320.24(a)
    - FDA's recommendations for meeting this requirement are reflected in PSGs
  - If no Q1/Q2 criteria included in the PSG, FDA will decline to provide a response

BE Approach Responses

- OGD has made a preliminary determination that, with respect to [formulation X],
  - the in-vitro approach to establishing BE as described in the [PSG] is suitable to support demonstration of BE for your proposed drug product.
  - the in vivo approach to establishing BE as described in the [PSG] is suitable to support demonstration of BE for your proposed drug product.

BE Approach Responses

- Ultimately, whether OGD receives an ANDA for substantive review will be determined during the filing review of the submitted ANDA.
- The approvability of your product will be determined during the scientific review of your ANDA.
- Any difference in physicochemical properties (e.g., viscosity, pH, osmolality) and commercial grades, in the test formulations has not been evaluated, and will be evaluated during the scientific review of the ANDA. Ultimately, it is the prospective applicant's responsibility to demonstrate that the selected commercial grades of ingredients would not affect the stability, performance, and BE of the final test formulation.
- OGD's determination does not take into consideration any differences in the concentration of active pharmaceutical ingredient(s) (APIs) between the test and reference formulations.

ADDITIONAL CONSIDERATIONS

Product Labeling Considerations

- If the results from your reverse engineering efforts seem to contradict what is listed in RLD labeling for a particular ingredient, we encourage you to share such information with FDA for consideration
- If you have evidence that an ingredient has been used in the RLD in a certain amount, we encourage you to provide that data to FDA
  - Help ensure accuracy of product labeling information and that drugs continue to be safe and effective
  - Support FDA's continual improvement of review processes and monitoring of FDA-approved products
  - Support generic drug development

General Summary

- FDA responses to questions involving drug formulations are limited by the Agency's obligations to protect the disclosure of trade secret information
- How FDA responds depends on:
  - The question being asked
  - Whether the drug product is required to be Q1/Q2 same by regulation
  - The information publicly available for the drug product
- FDA will indicate whether a drug formulation is Q1/Q2 same as the RLD for drugs intended for parenteral, ophthalmic, or otic use only
- If drug product is not intended for parenteral, ophthalmic, or otic use, FDA will provide preliminary feedback on the acceptability of the proposed BE approach based on the proposed formulation submitted


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