Navigating Formulation Assessments:
From General Q1/Q2 Inquiries to Supporting Complex Excipient Sameness

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 2: Excipient and Formulation Considerations

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Learning Objectives

- Describe Q1 (Qualitative) /Q2 (Quantitative) sameness
- Recognize the CFR requirements on generic formulations
- Evaluate bioequivalence (BE) approach and Q1/Q2
- Employ best practice of asking FDA Q1/Q2 questions and considerations when proposing a Q1/Q2 formulation

Complex generics still need to get the basics, like Q1/Q2, correct to reach approval

What is Q1/Q2?

- Q1/Q2 is a term referring to inactive ingredient assessments in abbreviated new drug applications (ANDAs)
- A proposed generic formulation is Q1/Q2 to its reference listed drug (RLD), if it contains
  - The same inactive ingredients (Qualitatively the same → Q1)
  - In the same concentration (Quantitively the same → Q2)

CFR Requirements on Generic Formulations

Section 314.94 Content and format of an ANDA

- (a)(9) Chemistry, manufacturing, and controls

➢ (ii) Inactive ingredients. Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant must identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.

➢ (iii)–(v) Specific inactive ingredient requirements for parenteral, ophthalmic, otic, and topical drug products, and changes permitted for such products

Q1/Q2 Sameness Assessments

- Q1: identity of an inactive ingredient.
  - An applicant should provide detailed information on the chemistry of each inactive ingredient, and characterization data, if needed for inactive ingredients.
- Q2: quantity of an inactive ingredient
  - An applicant should list the amount of all ingredients, except those used on an as needed (i.e., q.s.) basis, to a minimum of two decimal places and should be reported in % w/w and/or mg/mL.
    - Recommended that all ingredients are listed to the same number of decimal places (if more than two) and include calculation/equivalent amount for ingredients that may be added on a volume basis (e.g., mL/mL).
  - Q2 is the difference (%) of an inactive ingredient in the Test (T) and Reference (R) product (i.e., [(T-R)/R] x100).
  - Generally, FDA has interpreted Q2 sameness to mean a concentration that is within 95-105% of the RLD concentration.

Q1 Assessment of Complex Non-Compendial Excipients

- Additional comparative characterization of the proposed excipient and that of the RLD may be requested to support Q1 assessment of a novel and/or complex non-compendial excipient(s)
- For example, poly (D,L lactide-co-glycolide) (PLGA) is a non-compendial biodegradable random copolymer used as the rate controlling excipient in ~20 long-acting drug products
- Characterization should include polymer composition (L/G ratio), molecular weight, molecular weight distribution, structure (i.e., linear or star), end-cap/group, inherent viscosity, and glass transition temperature
- Provide justification that any differences would not impact the safety or efficacy of the generic drug as compared to the RLD

Q1 Assessment of Complex Non-Compendial Excipients (continued)

- Example of PLGA characterization data and analytical methods

Table1. the L:G ratio of the PLGA polymers determined by 1H-NMR

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

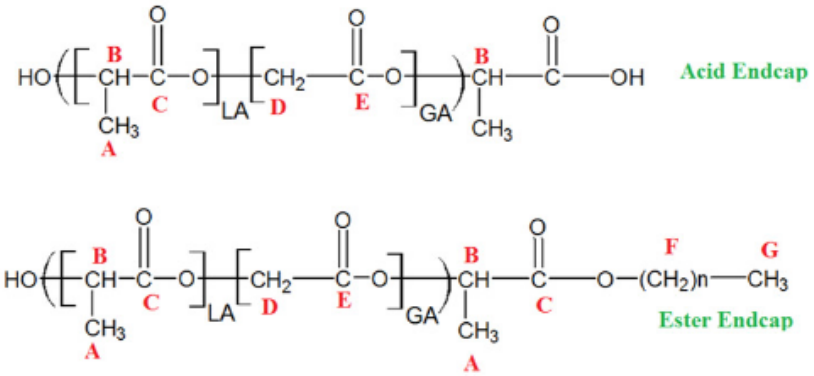
Table 2. Relative molecular weights measured by GPC

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

Table 3. Average intrinsic viscosity (IV) of PLGA polymers

Sample	IV (dL/g)
Test product	0.50
RLD product	0.49

Characterization of polymer L:G ratio, end cap, and structure



Outcomes from GDUFA-Funded Research

J. Garner, et al. "A protocol for assay of poly (lactide-co-glycolide) in clinical products." *International Journal of Pharmaceutics* 495.1 (2015): 87-92.

S. Skidmore, et al. "Complex sameness: Separation of mixed poly (lactide-co-glycolide)s based on the lactide: glycolide ratio." *Journal of Controlled Release* 300 (2019): 174-184.

J. Hadar, et al. "Characterization of branched poly (lactide-co-glycolide) polymers used in injectable, long-acting formulations." *Journal of Controlled Release* 304 (2019): 75-89.

J. Hadar, et al. "Method matters: Development of characterization techniques for branched and glucose-poly (lactide-co-glycolide) polymers." *Journal of Controlled Release* 320 (2020): 484-494.

Justifying Q2 differences

- In some instances an applicant may include additional information such as reverse engineering and/or rationale for why a proposed ingredient may not be within or limited to ±5% of a nominally listed amount. For example,
  - Ingredients for which variability in the RLD may be more than ±5%
    - Provide information to support this variability in the RLD and that the proposed amount in the test product is within the RLD range.
  - Buffers where the equilibrium ratio (concentration) of buffer components may not be within ±5% of the original amount of each component added
    - Provide information that the total buffer concentration (buffer capacity) of the test product is ±5% of the RLD and that the pH is similar.

Bioequivalence and Q1/Q2

- Criteria for a "Biowaiver" under **21 CFR 320.22**
  - **(b)(1):** The drug product is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and contains the same active and inactive ingredients in the same concentration (Q1/Q2) as the RLD product … …
  - **(b)(3):** The drug product is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form; … and contains no inactive ingredient or other change in formulation from the drug product … that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

Biopharmaceutics Classification System (BCS) Class 3 Biowaiver

- Guidance for Industry, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (December 2017)

  https://www.fda.gov/media/70963/download

- For BCS class 3 drug products, the following should be demonstrated
  - the drug substance is highly soluble
  - the drug product (test and reference) is very rapidly dissolving
  - the test product formulation is qualitatively the same (Q1) and quantitatively very similar ("Q2")

BCS Class 3 Biowaiver
What is “quantitatively very similar” ?

Quantitatively very similar includes the following allowable differences:

- Changes in the technical grade of an excipient
- Changes in excipients, expressed as percent (w/w) of the total formulation less than or equal to the following percent ranges:
  - Filler (± 10%)
  - Disintegrant, Starch (± 6%)
  - Disintegrant, Other (± 2%)
  - Binder (± 1%)
  - Lubricant, Calcium or Magnesium Stearate (± 0.5%)
  - Lubricant, Other (± 2%)
  - Glidant, Talc (± 2%)
  - Glidant, Other (± 0.2%)
  - Film Coat (± 2%)

Guidance for Industry, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (December 2017)
https://www.fda.gov/media/70963/download

Future Directions

- The BCS guidance is an example when the formulation sameness criteria differ from the “Q1/Q2 sameness” criteria for products required to be the same by regulations (e.g., 21 CFR 320.22(b))
- FDA often uses the “Q1/Q2 sameness” language for both situations
- We aspire to do better and provide more clarity about how the regulatory system works
  - Eligibility for alternate BE approaches: Primarily a scientific determination, regulations allow differences
  - Q1/Q2 sameness requirements by regulations: Constraint of the regulatory system, less allowance for difference even when scientifically appropriate

Clarifying Formulation Assessment for Products Not Required to be Q1/Q2

Drug products not required to be Q1/Q2 the same as the reference product for, such as topical dermatological products, may be eligible for a characterization-based BE approach when:

- The test product contains '**no difference**' in inactive ingredients[1] or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient:
  - The test product has similar physical and structural (Q3) characteristics to the reference product
  - The test product has an equivalent rate of drug release compared to the reference product
  - Evidence from in vitro studies support a demonstration of BE

1. For example, a Q1/Q2 formulation and/or an assessment supported comparison to the deformulated reference listed drug (RLD) or designated reference standard (RS) product.

Where to Ask Q1/Q2 Questions

- For parenteral, ophthalmic, and otic dosage forms where Q1/Q2 sameness is required by regulation, an applicant may submit a controlled correspondence to request a Q1/Q2 assessment for up to three proposed formulations
  - Draft Guidance for Industry, *Controlled Correspondence Related to Generic Drug Development* (November 2017) https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf
  - If co-packaged as product and diluent, a Q1/Q2 assessment is made on the entire drug product and not on the individual components

Where to Ask Q1/Q2 Questions (continued)

- For routes of administration where regulations **do not** require Q1/Q2 sameness
  - A non-Q1/Q2 application may be submitted to FDA, so sending controlled correspondence asking if a formulation is Q1/Q2 is **not** recommended (see Controlled Correspondence Guidance)
  - However, sometimes different BE approaches may be recommended in an FDA product-specific guidance (PSG) for a Q1/Q2 and non-Q1/Q2 formulation
    - You may submit a controlled correspondence asking if a proposed formulation is eligible for a particular BE approach

How to Ask Q1/Q2 Questions

If a formulation is required to be Q1/Q2 per 21 CFR 314.94 and may be eligible for "biowaiver" per 21 CFR 320.22, you may ask FDA:

- *If an application for your proposed generic formulation referencing Drug X is acceptable for filing as an ANDA; and*
- *If your proposed generic formulation referencing Drug X is eligible for a "biowaiver"*

How to Ask Q1/Q2 Questions (continued)

If a formulation is NOT required to be Q1/Q2 per regulation but a PSG or other guidance recommends that a proposed generic drug be "Q1/Q2" to demonstrate BE, you may ask FDA:

- *If you can follow the relevant PSG or FDA guidance approach using your proposed generic formulation*
- If no PSG or guidance is available, you may *propose a BE approach and ask FDA if it is acceptable to use such approach with your proposed generic formulation*

General Considerations for Q1/Q2

- Specify the quantitative amount of each inactive ingredient
- Specify the target value if the term “quantity sufficient” (q.s.) is used
- Specify the nominal amount, not including any overages
- Use matching names of compendial standards if such grade materials are used
- The amount of any inactive ingredient should not exceed the relevant limit in the FDA’s Inactive Ingredient Database
- Perform comparative characterizations on functional inactive ingredients if recommended by product-specific guidance

Special Considerations: pH Adjusters

- Currently pH adjusters are **not** "exception excipients"
- pH ranges in product specifications are often much wider than +/- 5% of the $[H_3O^+]$ or $[OH^-]$ concentration
- In the composition table, applicants have listed pH adjusters as
  - q.s. to a target pH value
  - A specific amount of pH adjuster
  - Multiple pH adjusters with logical operators "AND" or "OR"
- pH adjusters may not be listed in the RLD labeling but are used in the RLD product
- A specified minimum amount, potential range, and supporting justification may be requested for a pH adjuster that has an additional function in the formulation that requires a specific amount (e.g., solubilizer, in-situ converter)

Special Considerations: RLD Labeling

- If you believe there is an error in the RLD labeling or the FDA's response to your Q1/Q2 question
  - Provide detailed information (e.g., characterization data that detect a component not listed in the labeling, literature, etc.) that supports your position
  - Submit another controlled correspondence or a pre-ANDA meeting request

Summary

- Qualitative (Q1) and Quantitative (Q2) sameness refers to the same inactive ingredients (identity) and amounts (each within ±5%) to the RLD.
- Provide rationale and supportive data (e.g., comparative) for Q1/Q2 assessments that may include non-compendial excipients or variations outside the conventional Q1/Q2 paradigm.
- A bioequivalence approach may depend on the formulation sameness of the generic product to the RLD.
  - Solution drug products that are Q1/Q2 to the RLD are generally eligible for a waiver of in vivo bioequivalence testing. 21 CFR 320.22(b)(1) & (b)(3)
  - A quantitatively very similar immediate-release solid oral product may be eligible for a BCS waiver
  - A product-specific guidance may recommend an in vitro BE approach for a qualitatively and quantitatively similar product, e.g., Q1/Q2 or “no difference”.
- Take the BE approach into consideration when framing formulation assessment questions to the Agency.

Acknowledgement

- Office of Generic Drugs
  - Office of Research and Standards
    - Team of complex substances, complex injectables and implants, and ophthalmic products
    - Team of orally inhaled, nasal, and drug-device combination products
    - Team of topical dermatological and transdermal products
    - Team of immediate-release oral dosage form products
  - Office of Bioequivalence
  - Office of Generic Drug Policy
  - Office of Regulatory Operations
    - Division of Filing Review

Questions?

Challenge Question #1

For quantitative (Q2) sameness, ingredient amounts should be reported to __, and are assessed as acceptable if |[(T-R)/R] x100|is ≤ __:

A. Whole number, 5%

B. Whole number, 5.0%

C. Two decimal places, 5%

D. Two decimal places, 5.0%

Challenge Question #1

For quantitative (Q2) sameness, ingredient amounts should be reported to __, and are assessed as acceptable if |[(T-R)/R] x100|is ≤ __:

A. Whole number, 5%

B. Whole number, 5.0%

C. Two decimal places, 5%

D. Two decimal places, 5.0%

Challenge Question #2

Generic drug products that are solutions must be Q1/Q2 to the RLD to be eligible for submission as an ANDA:

A. True

B. False

Challenge Question #2

Generic drug products that are solutions must be Q1/Q2 to the RLD to be eligible for submission as an ANDA:

A. True

B. False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