

Navigating Q1/Q2 for Complex Generics

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Disclaimer



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Outline

- What is Q1/Q2
- CFR requirements on generic formulations
- Bioequivalence and Q1/Q2
- How to ask FDA Q1/Q2 questions

Complex generics still need to get “simple” things like Q1/Q2 correct to reach approval

What is Q1/Q2?

- Q1/Q2 is a term referring to inactive ingredient assessments in 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 (Quantitatively 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 Assessments

- Q1: identity of an inactive ingredient.
 - An applicant should provide detailed information on the chemistry and grade of each inactive ingredient, and characterization data, if needed for inactive ingredients.
- Q2: quantity of an inactive ingredient
 - Determine the difference (%) of an inactive ingredient in the Test (T) and Reference (R) products (i.e., $[(T-R)/R] \times 100$).
 - FDA's practice has generally been that differences of +/-5% are considered acceptable.

Where to Ask Q1/Q2 Questions



- For routes of administration where regulations require Q1/Q2 sameness
 - Sending questions via controlled correspondences is always acceptable

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 FDA’s guidance or regulation recommends different bioequivalence (BE) approaches for 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

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.

Bioequivalence and Q1/Q2 (continued)



Specific BE approaches may be recommended in product-specific guidance (PSG) for generic Q1/Q2 formulations

- Parenteral suspension, emulsion, and liposome*
- Ophthalmic ointment, suspension and emulsion*
- Otic suspension*
- Orally inhaled and nasal drug products (OINDPs)
- Topical dermatological products
- Oral drug products

* These product formulations must be Q1/Q2 per 21 CFR 314.94 with permitted changes

BE of Parenteral, Ophthalmic and Otic Products



- In vitro only BE option on Q1/Q2 formulation
 - Injectable suspension
 - Triamcinolone acetonide
 - Injectable emulsion
 - Fish oil; medium chain triglycerides; olive oil; soybean oil, olive oil; soybean oil
 - Injectable liposome
 - Perflutren, Sulfur hexafluoride lipid-type a microspheres
 - Ophthalmic suspension
 - Nepafenac, Dexamethasone/tobramycin, Prednisolone acetate, Loteprednol etabonate, Fluorometholone, Dexamethasone, Triamcinolone acetonide, Fluorometholone acetate
 - Ophthalmic ointment
 - Bacitracin, Erythromycin, Tobramycin
 - Ophthalmic gel
 - Timolol maleate, Loteprednol etabonate
 - Ophthalmic emulsion
 - Cyclosporine, Difluprednate
 - Otic suspension
 - Ciprofloxacin, Dexamethasone

**Data collected through
September 2019**

Current PSGs for OINDPs



DPIs

1. Acclidinium bromide
2. Albuterol sulfate
3. Budesonide
4. Fluticasone furoate
5. Fluticasone furoate; Vilanterol trifenate
6. Fluticasone propionate (2 PSGs)
1. Fluticasone propionate; Salmeterol xinafoate (2 PSGs)
8. Formoterol fumarate
9. Glycopyrrolate
10. Indacaterol maleate
11. Mometasone furoate
12. Salmeterol xinafoate
13. Tiotropium bromide
14. Umeclidinium bromide

**Q1/Q2 + In Vitro
+ In Vivo BE**

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MDIs

1. Albuterol sulfate
2. Beclomethasone dipropionate (2 PSGs)
3. Budesonide; Formoterol fumarate dihydrate
4. Ciclesonide
5. Fluticasone propionate
6. Fluticasone propionate; Salmeterol xinafoate
7. Formoterol Fumarate; Mometasone furoate
8. Ipratropium bromide
9. Levalbuterol sulfate
10. Mometasone furoate

**Q1/Q2 + In Vitro
+ In Vivo BE**

Nasal Solutions

1. Azelastine hydrochloride (2 PSGs)
2. Beclomethasone dipropionate
3. Calcitonin-salmon
4. Ciclesonide
5. Cyanocobalamin
6. Dihydroergotamine mesylate
7. Fentanyl citrate
8. Ketorolac tromethamine
9. Naloxone hydrochloride
10. Nicotine
11. Olopatadine hydrochloride
12. Oxymetazoline hydrochloride; Tetracaine hydrochloride
13. Sumatriptan
14. Zolmitriptan

**Q1/Q2 + In Vitro BE
OR
Non-Q1/Q2 + In Vivo BE**

Nasal Suspensions

1. Azelastine hydrochloride; Fluticasone propionate
2. Budesonide
3. Fluticasone furoate
4. Fluticasone propionate (2 PSGs)
5. Mometasone furoate monohydrate
6. Triamcinolone acetonide

**Q1/Q2 + In Vitro
+ In Vivo BE**

Data collected through
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BE of Topical Dermatological Products



- The test product contains no difference in inactive ingredients 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:
 - Topical dermatological solutions: biowaiver
 - Other topical dermatological products: characterization-based BE approach may be used
- Other BE options :
 - In Vivo Comparative Clinical Endpoint BE studies
 - In Vivo Pharmacodynamic (Vasoconstrictor) BE studies

BE and Q1/Q2 of Oral Drug Products



- Biopharmaceutics classification system (BCS) Class 3 Biowaiver
- Product specific guidances with in vitro option:
 - Acarbose Oral Tablets (8/2017)
 - Acyclovir Oral Buccal Tablets (9/2015)
 - Barium Sulfate Oral Paste (10/2017)
 - Barium Sulfate for Oral Suspension (2/2018)
 - Fidaxomicin Oral Tablets (8/2016)
 - Linaclotide Capsules (12/2018)
 - Miglitol Oral Tablets (6/2015)
 - Plecanatide Tablets (9/2019)
 - Sodium Phosphate Dibasic anhydrous & Sodium Phosphate Monobasic Monohydrate Oral Tablets (12/2012)
 - Sucralfate Oral Suspension (10/2017)
 - Vancomycin HCl Oral Capsules (12/2008)
 - Zolpidem Tartrate Oral Spray (4/2013)

**Data collected through
September 2019**

BCS Class 3 Biowaiver



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”)

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

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 ($\pm 10\%$)
 - Disintegrant, Starch ($\pm 6\%$)
 - Disintegrant, Other ($\pm 2\%$)
 - Binder ($\pm 1\%$)
 - Lubricant, Calcium or Magnesium Stearate ($\pm 0.5\%$)
 - Lubricant, Other ($\pm 2\%$)
 - Glidant, Talc ($\pm 2\%$)
 - Glidant, Other ($\pm 0.2\%$)
 - Film Coat ($\pm 2\%$)

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

Future Directions

- The BCS guidance gives an example of when the formulation sameness criteria for an alternate BE approach are not the same as the Q1/Q2 sameness criteria for products required to be the same by regulations
- Currently, FDA often uses Q1/Q2 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 requirements by regulations: Constraint of the regulatory system, less allowance for difference even when scientifically appropriate

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 CFR 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 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 $[H^+]$ 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 label but are used in the RLD product

Special Considerations: RLD label



- If you believe there is an error in the RLD label 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 label, literature, etc.) that supports your position
 - Submit another controlled correspondence or a pre-ANDA meeting request

Acknowledgement

- Office of Generic Drugs
 - Office of Research and Standards
 - Team of complex substance, 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?





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