Exploring Bioequivalence Considerations for Controlled Correspondences: Assessment and Best Practices

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Navigating Controlled Correspondences to
Support Generic Drug Development
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Learning Objectives

1. Describe types of controlled correspondences (CCs) assessed by the Office of Bioequivalence.
2. Distinguish differences between Level 1 versus Level 2 CCs.
3. Understand practices for submitting CCs that are often received by the Office of Bioequivalence.
    1. Inactive Ingredient Evaluation
    2. Use of a reference standard (RS) that is not listed in the Orange Book.
    3. Prior Approval Supplements

CCs Assessed by the Office of Bioequivalence

Queries that the Office of Bioequivalence Reviews

- Adding an Additional Strength
- Evaluation of Inactive Ingredients
- Alcohol Dose Dumping
- Use of an RS Other Than That Listed in the Electronic Orange Book
- Skin Blanching and Vasoconstrictor Studies
- Cross Referencing an ANDA BE Study
- Retention Sample Requirements
- Comparative Dissolution Testing
- Pre-Approval or Post-Approval Changes
- Determination of Study Conduct and/or Design

*Not an exhaustive list

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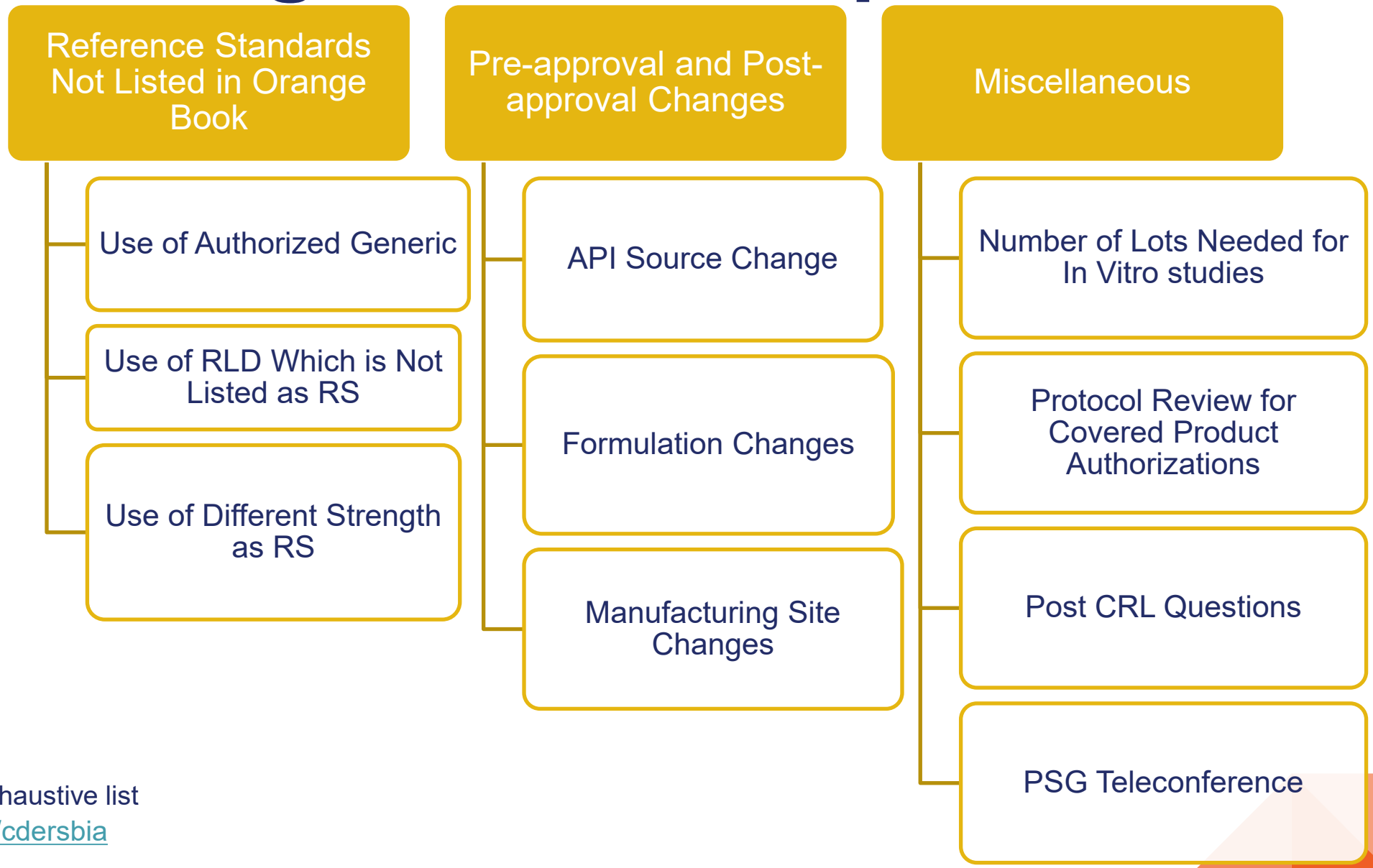
Subcategories: A Deeper Dive



*Not an exhaustive list

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Level 1 versus Level 2 CCs

Level 1 Versus Level 2 Designation

- Level 1 referred to as a standard CC in GDUFA II commitment letter.
- Level 2 referred to as a complex CC in GDUFA II commitment letter.
- CCs that automatically receive a Level 2 Designation:
  - Questions that involve evaluation of clinical content
  - Covered product authorizations
  - Alternate BE approaches
- Per the guidance for industry, *Controlled Correspondence Related to Generic Drug Development:*
  - Level 1 CCs are to be reviewed in 60 calendar days.
  - Level 2 CCs are to be reviewed in 120 days.
- Level 1 CC can be switched to a Level 2 if input is required from other Offices within the Agency.

Best Practices

Inactive Ingredient Evaluation

- Queried amounts for inactive ingredients are evaluated in all populations (i.e., adult and pediatric) that the drug is indicated for.
- Maximum daily exposure (MDE) justification based on a previously FDA-approved drug product (**NDA or ANDA**) for the same route of administration and similar context of use.
- Clinical or toxicological data used as justification is outside the scope of review.

Inactive Ingredient Evaluation Continued

- The number of allowed queries is specified within the *Controlled Correspondence Related to Generic Drug Development* (March 2024)
  - "Three and Three recommendation"
  - Three inactive ingredients with one amount each or one inactive ingredient with three amounts each
  - Routes of administration
  - Drug product that is dosed based on ranges (e.g., weight or age), each "range" equates to 1 evaluation.
    - For adult and pediatric population
- Inactive ingredient with multiple components (e.g., flavors)
  - Acceptability of components does not guarantee overall acceptability for inactive ingredient.

Example 1: Inactive Ingredient

- Evaluation of one amount for Disodium Hydrogen Phosphate Dihydrate in Phytonadione Injectable Emulsion, 10 mg/ml.
  - Administered intravenously, intramuscularly, or subcutaneously to adults and the pediatric population.
- "Three and Three recommendation": Assessed amount of Disodium Hydrogen Phosphate Dihydrate for all three routes of administration in adults.
- Applicant informed to submit separate CCs for varying routes of administration in pediatrics.
  - In alignment with *Controlled Correspondence Related to Generic Drug Development (March 2024)*

Example 2: Inactive Ingredient

- Evaluation of an amount for Sucrose, Xanthan Gum and Polysorbate 80 respectively in Ibuprofen Oral Suspension, 100 mg/5ml.
- Ibuprofen Oral Suspension is indicated for children 2-11 years of age.

Weight (lb)	Age (yr)	Dose (mL)
Under 24	Under 2 years	Ask doctor
23-35 lbs	2-3 years	5 mL
36-47 lbs	4-5 years	7.5 mL
48-59 lbs	6-8 years	10 mL
60-71 lbs	9-10 years	12.5 mL
72-95 lbs	11 years	15 mL

Example 2 Continued: Inactive Ingredient

- Five dosage ranges based on weight and age and three separate amounts for three ingredients.
- Each inactive ingredient was evaluated at the 23-35 lbs (2-3 year) range.
- Applicant informed to submit CC for further evaluations in pediatric population.
  - In alignment with *Controlled Correspondence Related to Generic Drug Development*

Use of an RS that is not listed in Electronic Orange Book

- RS is drug product selected by FDA to demonstrate bioequivalence for intended ANDA.*
  - Usually, the RLD.
  - If RLD is not available, a previously approved ANDA can be designated as the RS.
- The Orange Book designates/assigns an RS.
- If RS (RLD or designate ANDA) is not available on the market. The Office of Bioequivalence can:
  - Suggest another approved ANDA for BE determination.
  - Provide an alternate BE approach (e.g., PK between two different dosage forms) if another approved ANDA is not available.

Guidance for Industry: Referencing Approved Drug Products in ANDA Submissions* (October 2020).

Example 3: Use of an RS not Listed in the Orange Book

- Development of Primidone Oral Suspension, 250 mg/5 ml.
- RLD discontinued.
- No RS or any approved ANDA for Primidone Oral Suspension.
- Alternate BE approach.
  - Applicant sought to use Primidone Immediate Release Tablets, 50 mg for *in vivo* studies.
  - A PK bridge could be drawn between the Tablets and Oral Suspension from the New Drug Submission.
  - Applicant was informed that utilizing Primidone Tablets as an RS to demonstrate bioequivalence to Primidone was reasonable.

Changes to Approved ANDAs via Prior Approval Supplements

- Manufacturing sites or formulation
  - SUPAC IR, SUPAC MR, and SUPAC SS provide recommendations for bioequivalence documentation needed to support changes.
  - Recommendations for other products (e.g., nasal sprays) do not fall under the prior guidances and may require other studies to support changes.
- API source
- Addition of a new strength

Changes to Approved ANDAs via Prior Approval Supplements Continued

- Changes that necessitate an *in vivo* study should utilize the current reference standard.
- Conditions under which an in vivo study should be conducted (i.e., fasting or fed) can be confirmed through the CC response.

Example 4: Addition of a New Strength via Prior Approval Supplement

- Addition of a 1 g strength by current applicant (Company A) to an approved ANDA which already has a 500 mg strength and 750 mg strength.
- The 500 mg and 750 mg strength of the RLD are discontinued.
- A 750 mg strength for Company B's ANDA is the current RS.
- Company C has an ANDA for a 1 g strength approved via a suitability petition.
- The Product Specific Guidance for the drug product recommends fasting study on 750 mg strength.
- Company A requested biowaiver for their proposed 1 g strength.
- Biowaiver deemed unacceptable
  - In vivo study recommended comparing Company A's intended 1 g strength to Company C's approved 1 g strength.

Challenge Question 1

- Which scenario counts as one evaluation for an Inactive Ingredient Controlled Correspondence?
  a. An MDE from dosage range based on weight
  b. An MDE from dosage range based on age
  c. An MDE for a single component of an inactive ingredient
  d. All of the Above

Challenge Question 2

True or False: The reference listed drug (RLD) is discontinued, and the current reference standard is not available on the market. I should petition the Office of Bioequivalence to designate a reference standard.

Food For Thought

- Remember the “3 and 3 recommendation” when submitting inactive ingredient queries.
- An alternate BE approach may be possible if the RS (RLD or approved ANDA) is not available on the market.
- Prior approval supplements for changes that necessitate an *in vivo* BE study should utilize the RLD or RS.

Resources

- Guidance for Industry: Controlled Correspondence Related to Generic Drug Development (Final, March 2024)
- Guidance for Industry: SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (Final, November 1995)
- Guidance for Industry: SUPAC –MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (Final, October 1997)
- Guidance for Industry: Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (Final, May 1997)
- Guidance for Industry: Handling and Retention of Bioavailability BA and Bioequivalence BE Testing Samples (Draft, March 2024)

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Questions?

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