Overview of Controlled Correspondence:
GDUFA III Updates and a Comprehensive Analysis of Controlled Correspondence Received by the Office of Bioequivalence

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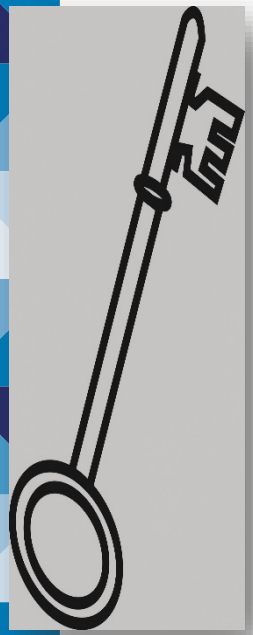
SBIA Generic Drug Forum – April 10-11, 2024

The Key to Access (Get it?)



- Objective
- Resources
- GDUFA III
- Best Practices
- Common Issues/Deficiencies
- Other Considerations

Learning Objectives

- Define and categorize controlled correspondence
- Review common controlled correspondence content
- Distinguish characteristics of Valid correspondence
- Uncover reasons for Not Valid correspondence

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Controlled Correspondence Defined in GDUFA III

Two Types of Controlled Correspondences:

- Level 1 (Standard in GDUFA II)
- Level 2 (Complex in GDUFA II)
- *Other - Clarification of Ambiguity*

Post-CRL Controlled Correspondence

- Seeking regulatory and/or scientific advice
- CRL for ANDA or Supplement Issued After October 1, 2022
- CRL and cited deficiency

Q1/Q2 Evaluation Controlled Correspondence

- One strength per controlled correspondence
- Three formulations per controlled correspondence
- Avoid ranges
- Composition should reflect ANDA submission

Inquiries Related to a Specific Pending ANDA

- New strength
- New package
- Advice to address deficiency in CRL
- Feedback after product specific guidance Tcon
- Covered Product Authorization (CPA)

What to Include in a Controlled Correspondence

- Documents on corporate letterhead
- Complete contact information
- Letter of Authorization (if applicable)
- Reference listed drug (RLD)

What to Include in a Controlled Correspondence (cont'd)

- Previous related controlled correspondence
- Prior relevant research
- Recommended review discipline
- Future OGD submission
- Specific questions

Challenge Question #1

What information should be submitted in a controlled correspondence?

A. Cover letter on business letterhead.

B. Previous controlled correspondence accepted for substantive review that is related.

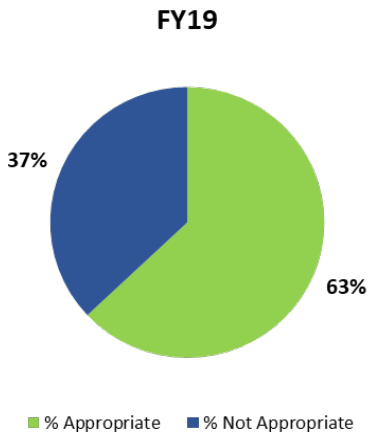
C. Statement indicating controlled correspondence will lead to a future submission to OGD.

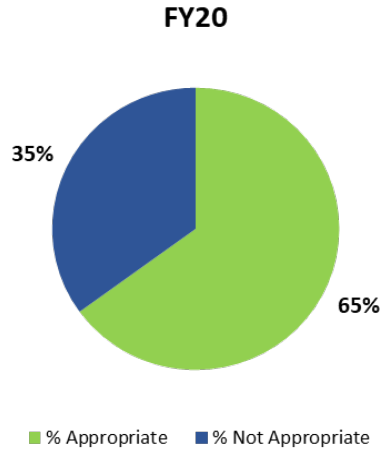
D. A, B, and C.

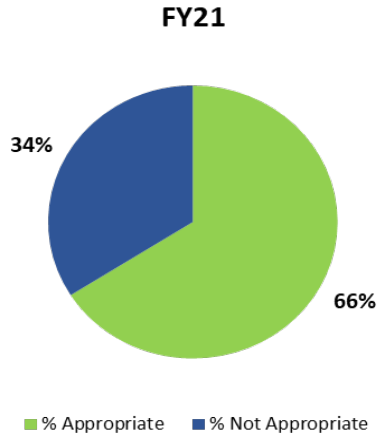
Common Reasons Controlled Correspondence are Not Valid

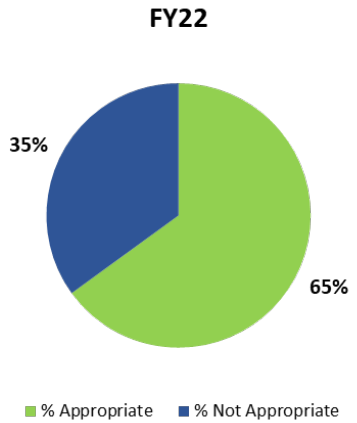
- Missing/Expired Letter of Authorization (LOA)
- Q1/Q2 do not reflect ANDA submissions
- BE Guidance Does Not Exist – Not a Valid Control
- Incomplete submissions

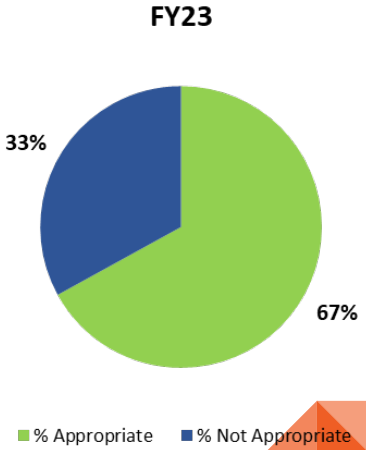
Percentage Valid vs Not Valid FY19 to FY23











Challenge Question #2

What is one common reason that controlled correspondence is considered Not Valid?

A. More than five submissions in one day.

B. U.S. Agent represents more than one applicant.

C. U.S. Agent (for U.S. applicant) is in the United States.

D. Reference Standard (RS) is selected in the CDER NexGen Portal instead of Reference Listed Drug (RLD) because RLD is discontinued in Orange Book.

Resources

- **Controlled Correspondence Draft Guidance Link (December 2022):**

https://www.fda.gov/media/164111/download

- **GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (GDUFA III Commitment Letter)**

https://www.fda.gov/media/153631/download

Resources

- **OGD Website:**

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm142112.htm

- **GDUFA III Webpage:**

https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-iii

- **Recorded Presentation Highlighting Important GDUFA III Changes Related to Controlled Correspondence (October 2022)**

https://youtube/https://www.youtube.com/watch?v=wfsb6Vvn0eg

Summary

- Defined controlled correspondence
- Content review
- Best practices with submissions

Closing Thought

To make your Controlled Correspondence easier, keep a copy of the *Guidance* handy and **watch our YouTube videos**.

An Overview of Controlled Correspondence Part II: A Comprehensive Analysis of Controlled Correspondences Received by the Office of Bioequivalence

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SBIA: Generic Drugs Forum – April 10-11, 2024

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

Learning Objectives

- Describe the main categories of controlled correspondence (CC) reviewed by the Office of Bioequivalence (OB)
- Understand the scientific rationale of the Agency's responses to questions under the major CC categories

OB's CC Review Responsibilities*

- OB reviews CCs containing inquiries related to the planning of bioequivalence (BE) studies.
- OB also reviews questions related to the maximum daily exposure of an inactive ingredient.
- In addition, OB reviews CCs when applicants want to add an additional strength to their approved product line and request feedback on whether they should conduct the studies recommended in the product-specific guidance for the additional strength.

* Guidance for Industry: Controlled Correspondence Related to Generic Drug Development (March 2024)

Three Major CC Categories Reviewed by OB

A survey of all 903 CCs received by the Office of Generic Drugs (OGD) from April 2021 to March 2023 and assigned to OB:

1. Maximum Daily Exposure of Inactive Ingredients (759 CCs)
2. Retention Samples Related to in vivo Pharmacokinetic (PK) BE and in vitro BE Studies (43 CCs)
3. Other BE Study-Related Questions (101 CCs)

Other BE Study-Related Questions

Categories for BE Questions	Subcategories	# of CCs
Use a Different RS Other Than the One Recommended in the Orange Book	Use Authorized Generic, RLD, another Approved ANDA, or a Different Strength from RS (A)NDA as RS	17
No approved drug available as RS		17
BE Questions Related to Post-approval Changes	API Source Change; BE study when Exhibit Batch Is Not Acceptable; Formulation Change: BE Study; Formulation Change: inactive ingredient; Formulation Change: Q1/Q2; Manufacturing Site Change; Multiple Changes: BE study; Reactivate a Withdrawn Approved ANDA with BE Related Questions (for Post-approval Only)	16
BE Questions Related to Pending ANDAs		5
Alcohol Dose Dumping	The Need for an Alcohol Dose Dumping Test; Test Conditions	14
BE Questions for Adding an Additional Strength		8
Comparative Dissolution Testing	Waiver; Deem BE; SUPAC; Failed Dissolution Testing (e.g., f2<50)	6
Others	Bioanalysis of BE Study Samples; BE Questions for a Repeated / Failed Study (e.g., Using a Different Lot for a Repeated Study); # of Lots / Units for In Vitro BE Study	18

RLD: reference listed drug; RS: reference standard; ANDA: abbreviated new drug application; API: active pharmaceutical ingredient; Q1: qualitative the same; Q2: quantitative the same; SUPAC: scale-up and post-approval changes

Use a Different RS Other Than the One Recommended in the Orange Book

- RS Definition and RS Selection
- Use an Authorized Generic as RS?
- Use the RLD as RS?
- Use Another Approved ANDA as RS?
- Use a Different Strength from RS (A)NDA as RS?

No Approved Drug Available as RS

- Use a Different Dosage Form Containing the Same Drug Substance as a Bridge?
- Use Two Individual Drug Products as a Bridge for Fixed-dose Combination Product?

Challenge Question

Which one of the following CCs is NOT reviewed by the Office of Bioequivalence:

A. Alcohol Dose Dumping

B. Maximum Daily Exposure of Inactive Ingredients

C. User interface of drug-device combination products

D. Retention Samples Related to in vivo PK BE and in vitro BE Studies

Summary

- OB reviews a wide range of CCs, such as questions related to the planning of BE studies or the maximum daily exposure of an inactive ingredient.
- Understanding the scientific rationale of CC responses can potentially reduce the number of CCs and facilitate generic drug development.

Acknowledgement

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Questions?

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