

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

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# The Key to Access (Get it?)



Objective



Resources

3

GDUFA III



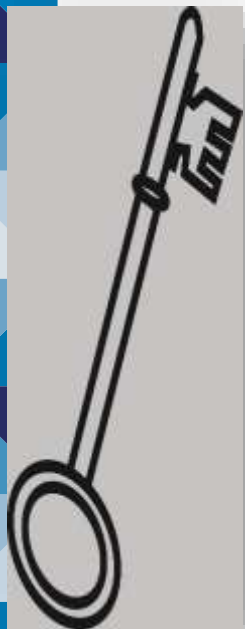
Best Practices



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



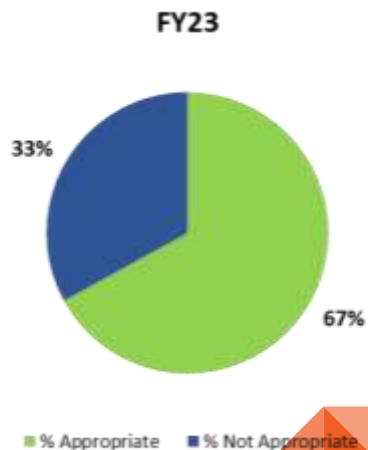
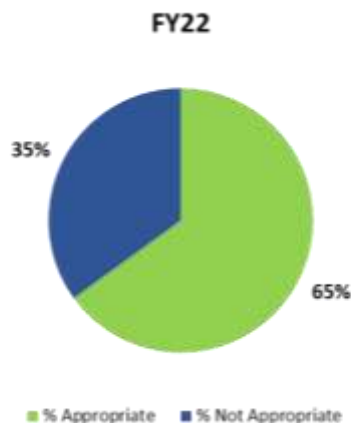
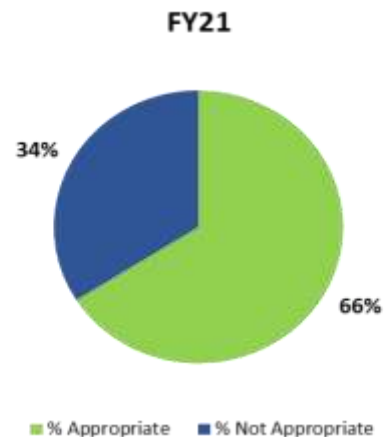
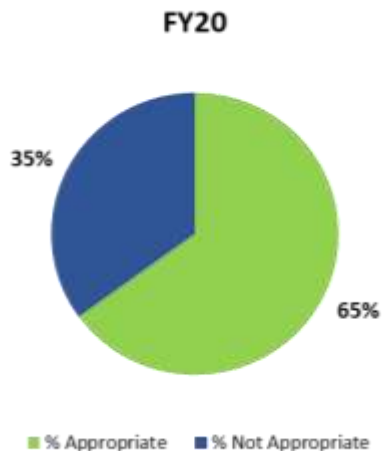
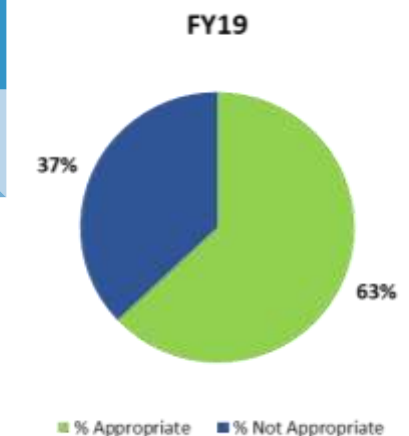
**What information should be submitted in a controlled correspondence?**

- 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.

# 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;	16
BE Questions Related to Pending ANDAs	Multiple Changes: BE study; Reactivate a Withdrawn Approved ANDA with BE Related Questions (for Post-approval Only)	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., $f_2 < 50$ )	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

# 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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ADMINISTRATION

# Questions?

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