Controlled Correspondence

Minimizing Rejections, Maximizing Results

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Learning Objectives

- Define and categorize controlled correspondences
- Understand submission requirements
- Avoid Common Mistakes
- Provide Resources

Controlled Correspondence Defined

Two Types of Controlled Correspondences:

- Level 1 (FDA responds to 90% within 60 calendar days of the date of submission)
- Level 2 (FDA responds to 90% within 120 calendar days of the date of submission)

Level 1 Controlled Correspondence

The GDUFA III commitment letter defines *level 1 controlled correspondence* as correspondence submitted to the Agency, by or on behalf of a generic drug manufacturer or related industry:

1. Requesting information on a specific element of generic drug product development:
   a. Before ANDA submission;
   b. After a Product-Specific Guidance (PSG) Teleconference if a prospective applicant or applicant seeks further feedback from FDA;
   c. After issuance of a complete response letter (CRL) or tentative approval;
   d. After ANDA approval

2. Concerning post approval submission requirements that are not covered by Center for Drug Evaluation and Research (CDER) post approval changes guidance and are not specific to an ANDA.

Level 2 Controlled Correspondence

The GDUFA III commitment letter defines *level 2 controlled correspondence* as correspondence that meets the definition of level 1 controlled correspondence and:

1. Involves evaluation of clinical content;
2. Requests a Covered Product Authorization and review of bioequivalence (BE) protocols for development and testing that involves human clinical trials for an ANDA where the reference listed drug (RLD) is subject to a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU);
3. Requests a Covered Product Authorization to obtain sufficient quantities of an individual covered product subject to a REMS with ETASU when development and testing does not involve clinical trials;
4. Requests evaluations of alternative BE approaches (e.g., pharmacokinetic, in vitro, clinical);
5. Requires input from another office or center.

Submitting Controlled Correspondences

- Controlled Correspondence should be dated and submitted within 7 days of the date on the correspondence
- Controlled Correspondence should be on corporate letterhead.
- Name, title, address, email, phone number, and entity (e.g., corporate affiliation) of the person submitting the controlled correspondence.

Submitting Controlled Correspondence

- There should be a statement in the controlled correspondence that the submission is related to either a potential ANDA submission to OGD, an ANDA that is pending with FDA, an ANDA that received a CRL, an ANDA that received tentative approval, or an approved ANDA.
- Include the complete RLD information - including application number, proprietary (brand) name, manufacturer, active ingredient/established name, dosage form, route of administration, and strength(s).

Submitting Controlled Correspondence

- Controlled Correspondence should cite a product in the Orange Book or to an approved suitability petition
- Include the docket number for the approved suitability petition if the product is not in Orange Book.

Challenge Question #1

- A controlled correspondence should be dated and submitted within 14 days of the date on the correspondence.

- A) TRUE
- B) FALSE

Maximum Daily Dose (MDD) of Drug Product

- OGD will **confirm** MDD of drug products, but it is the responsibility of the requestor to propose the MDD of the drug product for OGD to consider.
- We request that you provide us with the MDD determination and information supporting this determination (e.g., information from literature searches, drug information services, approved labeling, pharmacology review of the Summary Basis of Approval for the RLD, calculations, etc.)

MDD of Inactive Ingredients (IIG)

- You should submit no more than 3 levels for evaluation
  - 1 IIG with 3 levels
  - 3 IIGs with 1 level each
  - 1 IIG with 2 levels and 1 IIG with 1 level
- Inactive ingredient assessment requests should be submitted in a table format.

Inactive Ingredient Name	Grade	UNII	Amount/ unit (mg)*	Total Daily Intake (TDI) based On Maximum Daily Dose**	IID Limit, Route; Dosage Form

*For each strength of proposed drug product

**List only the highest proposed level/MDD combination

- You should not include pharmacology/toxicology data to support a level of an IIG.
- You should not include the full formulation. Include only the inactive ingredient(s) in question.

Qualitative/Quantitative (Q1/Q2) Sameness

- Include salt and hydration forms, purity, grade or type, and function for each ingredient.
- The units of measure should be consistent throughout the formulations.
- No more than 3 formulations should be included in a controlled correspondence. Only one Q1/Q2 controlled correspondence for each strength will be reviewed at one time.
- Submit a separate inquiry for each strength. Different fill volumes are considered different strengths.
- Submit a separate inquiry for each presentation – syringe and vial should be submitted separately.
- OGD will not review additional formulations or duplicate formulations for evaluation after a formulation has already been reviewed and found acceptable for ANDA filing.

Formulation Evaluation for Products based on posted Product Specific Guidance (PSG)

- FDA's guidances (e.g., PSGs) sometimes recommend specific BE approaches that may be suitable when the formulation components and composition of the proposed generic drug product meet specified criteria for sameness or for no significant difference relative to that of the reference standard, which ordinarily is the RLD.
  - In these instances, requestors can submit a controlled correspondence to ask **whether one or more proposed formulation(s) may be suitable for the specific BE approach recommended in FDA's guidance.** This should not be a request for Q1/Q2 sameness.
- Should not reference Q1/Q2 sameness or request a Q1/Q2 evaluation for products where Q1/Q2 sameness is not required by regulation or specifically required to follow the option recommended in the PSG.

Post Approval ANDA Specific Controlled Correspondence

- Choose the RLD in the Portal which was the basis of submission for the approved ANDA.
- For an approved ANDA, you should not enter your approved ANDA as the RLD Product information in the Portal.
- Reference your approved ANDA in the cover letter and enter the approved ANDA information when asked in the Portal if the inquiry is related to a submitted or pre-assigned ANDA.

Previous, Related Controlled Correspondences

- Include previous, related controlled correspondences accepted for substantive review and response and the Agency's response. Include any information requests sent by the Agency and responses to information requests.
- You should not reference or include copies of controlled correspondences that have not been responded to or that are pending.
- You should not include multiple copies of previous, related controlled correspondences.
- You should not include controlled correspondences that are not related to your current inquiry.
- You should not include copies of controlled correspondences that were not accepted for substantive review and response.

Challenge Question #2

- Controlled Correspondence should include:

A. Any information requests sent by the Agency and responses to information requests.

B. Multiple copies of previous, related controlled correspondences.

C. Controlled Correspondences that are not related to your current inquiry.

D. Reference or include copies of controlled correspondences that have not been responded to.

Post-CRL Controlled Correspondence

- Include a copy of the CRL.
- Clearly identify the deficiency related to the controlled correspondence in the cover letter.
- Inquiries that are not related to a deficiency in a CRL will not be accepted as a valid control.
- You may submit inquiries regarding nitrosamines for CRLs issued prior to 10/1/22 and pending ANDAs.

Pending ANDA Controlled Correspondence

- Pending ANDA Exceptions:
  - New strength development
  - Different package configuration
  - Covered Product Authorization (CPA) requests
  - Requests for RLD designation/RS designation
  - Inquiries regarding nitrosamines.

Letter of Authorization (LOA)

- LOA should be on corporate letterhead.
- LOA should be dated within 1 year of date of submission.
- Include the full contact information for both the company the authorized agent is representing and the authorized agent (company name, title, address, phone number and e-mail).
- If an authorized agent is submitting the controlled correspondence, include a copy of a letter of authorization with each controlled correspondence, regardless of whether the prospective applicant or applicant is in the United States.

Covered Product Authorization (CPA) Request

- For CPA requests not subject to testing in humans
  - You should specify that the samples will not be for human use if you are requesting a CPA that will not be used for in vivo BE studies.

- For CPA requests for drug products for human use with BE study protocols:
  - You should specify that the samples will be for human use and ensure the following documents are attached -
    - Protocols, and Informed Consent Documents

Device Evaluation Request

- You should not submit a controlled correspondence requesting the evaluation of a device until the test device and RLD device has been received by the agency.
- Send the test and RLD devices (without a required signature) to the address below for evaluation purpose.

Office of Research and Standards/Office of Generic Drugs
Attention: Kris Andre
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Building 75, Room 1694
Silver Spring, MD 20993

- Once you have received confirmation that the test and RLD devices have been received, please submit your controlled correspondence through the CDER NextGen Portal and include the tracking information for the devices in your cover letter.

*** Device samples do not need to be sent under temperature-controlled conditions.

*** Only one device prototype will be reviewed per submission. Multiple device prototypes will not be reviewed concurrently.

Challenge Question #3

- The letter of authorization should:

A. Be on corporate letter head

B. Be dated within one year of the submission date

C. Contain full contact information: company name, title, address, phone number and e-mail.

D. All of the Above

Active Pharmaceutical Ingredient (API)

- The API is not evaluated during a Q1/Q2 sameness. If a formulation is required to be Q1/Q2 to the RLD, please submit a request for Q1/Q2 sameness prior to submitting an inquiry about the API.
- After OGD confirms your formulation is Q1/Q2 with respect to the inactive ingredients, you may submit a new controlled correspondence regarding the active ingredient in your proposed formulation.

Clarification of Ambiguities

- Requests to clarify are submitted to seek clarification of ambiguities in the Agency's response and should not be a request to review new or additional information. Clarification requests should not be used to provide clarification of your original request.
- You should submit your clarification request documents to the original Event ID. Do not submit as a new controlled correspondence.
- You should submit within 7 calendar days of the Agency's response to the original submission.
- You should include the original controlled correspondence and Agency's response, and any information requests associated with the controlled correspondence.
- If you are submitting on behalf of an applicant, you should include a letter of authorization.

Waiver Requests

- OGD will not pre-review BE waiver requests as a controlled correspondence. BE waiver requests must be submitted with the ANDA.
- OGD will not pre-review BCS class I waiver requests.
- OGD will review requests seeking confirmation that an ANDA would be eligible for a BCS class III biowaiver.

Data Entry into Portal

- Choose the RLD in the Portal even if the RLD is in the discontinued section of Orange Book.
- The company name for the Applicant and U.S. Agent should be consistent throughout the submission. The names should be the same in the Portal, letter of authorization, and the cover letter.
- When submitting as a U.S. Agent, after selecting “Yes”, you should be entering the information for the company who you are submitting on behalf of and not your own information.

Challenge Question #4

- In a Clarification of Ambiguity request you may ask FDA to review new or additional information or ask follow-up questions of the Agency's response.

- A) TRUE
- B) FALSE

Resources

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

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

- **How To Obtain a Covered Product Authorization Guidance for Industry**

https://www.fda.gov/media/161730/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://www.youtube.com/watch?v=wfsb6Vvn0eg