Controlled Correspondence Related to Generic Drug Development

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Lisa Bercu 240-402-6902.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2022
Generic Drugs

Revision 1

Controlled Correspondence Related to Generic Drug Development

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
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Controlled Correspondence Related to Generic Drug Development Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information regarding the process by which generic drug manufacturers and related industry or their representatives can submit to FDA controlled correspondence requesting information related to generic drug development. This guidance also describes the Agency's process for providing communications related to such correspondence.

This guidance revises the guidance for industry *Controlled Correspondence Related to Generic Drug Development* issued in December 2020. When final, this guidance will replace the December 2020 guidance. The December 2020 guidance was issued as part of FDA's implementation of the Generic Drug User Fee Amendments of 2017 (GDUFA II).[2] This guidance is being issued to incorporate program enhancements related to the review of controlled correspondence to which FDA committed, and industry agreed, as part of their negotiations relating to the reauthorization of the Generic Drug User Fee Amendments (GDUFA) (GDUFA III),[3] as described in "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027" (GDUFA III commitment letter).[4] Other significant changes from the December 2020 version include providing additional recommendations for specific types of inquiries in controlled correspondence.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] FDA Reauthorization Act of 2017 (Public Law 115-52).

[3] See Division F, Title III, of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023 (Public Law 117-180).

[4] The GDUFA III commitment letter is available at https://www.fda.gov/media/153631/download.

as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

The Generic Drug User Fee Amendments of 2012 (GDUFA I)[5] amended the Federal Food, Drug, and Cosmetic (FD&C) Act to authorize FDA to assess and collect user fees to provide the Agency with resources[6] to help ensure patients have access to quality, affordable, safe, and effective generic drugs. GDUFA fee resources bring greater predictability and timeliness to the review of generic drug applications. GDUFA has been reauthorized every 5 years to continue FDA's ability to assess and collect GDUFA fees, and this user fee program has been reauthorized two times since GDUFA I, most recently in the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023.[7] As described in the GDUFA III commitment letter applicable to this latest reauthorization, FDA has agreed to performance goals and program enhancements regarding aspects of the generic drug assessment program that build on previous authorizations of GDUFA. New enhancements to the program are designed to maximize the efficiency and utility of each assessment cycle, with the intent of reducing the number of assessment cycles for abbreviated new drug applications (ANDAs) and facilitating timely access to generic medicines for American patients.

As further discussed in this guidance, FDA agreed to certain goals and procedures for the review of controlled correspondence received on or after October 1, 2022.[8] Specifically, the Agency agreed that:

- FDA will review and respond to 90 percent of level 1 controlled correspondence[9] within 60 calendar days of the date of submission.

[5] Title III of the Food and Drug Administration Safety and Innovation Act, Public Law 112-144.

[6] User fees are available for obligation in accordance with appropriations acts.

[7] See Division F, Title III, of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023 (Public Law 117-180).

[8] Starting October 1, 2022, FDA will respond to all controlled correspondence submitted before ANDA submission, during an ANDA assessment cycle to seek further feedback from FDA after a product-specific guidance teleconference or to seek a Covered Product Authorization, after tentative approval, and after ANDA approval. FDA also intends to respond to controlled correspondence submitted after issuance of a complete response letter as long as the complete response letter was issued on or after October 1, 2022.

[9] Level 1 controlled correspondence was called "standard controlled correspondence" in the GDUFA II commitment letter.

- FDA will review and respond to 90 percent of level 2 controlled correspondence[10] within 120 calendar days of the date of submission.

- FDA will review and respond to 90 percent of submitter requests to clarify ambiguities in the controlled correspondence response within 21 calendar days of FDA's receipt of the request.[11]

Consistent with FDA's other user fee programs, FDA will calculate the goal date from the day after a submission.[12]

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; or

2. Concerning postapproval submission requirements that are not covered by Center for Drug Evaluation and Research (CDER) postapproval changes guidance and are not specific to an ANDA.[13]

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

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[10] Level 2 controlled correspondence was called "complex controlled correspondence" in the GDUFA II commitment letter.

[11] GDUFA III commitment letter at 11. See also the definition of *days*, which "unless otherwise specified, means calendar days" (id. at 47).

[12] GDUFA III commitment letter at 4. Also, refer to FDA's guidance for industry *Providing Regulatory Submissions in Electronic Format — Receipt Dates* (Feb. 2014) for information on how FDA calculates receipt dates for regulatory submissions in electronic format, including controlled correspondence. As described in that guidance, controlled correspondence will be received by the Agency Monday through Friday from 12:00 a.m. to 11:59 p.m. Eastern Standard Time/Eastern Daylight Time, excluding Federal holidays and days when the FDA office that will review the correspondence is closed. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[13] GDUFA III commitment letter at 46.

1. Involves evaluation of clinical content;

2. Requests a Covered Product Authorization[14] 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); or

5. Requires input from another office or center.[15]

This guidance provides additional detail and recommendations concerning:

- What inquiries FDA considers to be controlled correspondence for the purposes of meeting the Agency's agreements under the GDUFA III commitment letter
- What information requestors should include in a controlled correspondence to facilitate FDA's consideration of and response to a controlled correspondence
- What information FDA will provide in its communications to requestors that have submitted controlled correspondence
- How requestors can submit requests to clarify ambiguities in FDA's controlled correspondence responses and the Agency's process for responding to those requests

III. CONTROLLED CORRESPONDENCE

[14] A *Covered Product Authorization* is a letter from FDA authorizing an eligible product developer to obtain sufficient quantities of an individual covered product subject to a Risk Evaluation and Mitigation Strategy with Elements to Assure Safe Use for product development and testing purposes, as described in section 610 of Division N of the Further Consolidated Appropriations Act, 2020 (21 U.S.C. 355-2), commonly referred to as the "CREATES Act" (GDUFA III commitment letter at 47). For further information on how to obtain a Covered Product Authorization, see FDA's draft guidance for industry, *How To Obtain a Covered Product Authorization* (Sep. 2022). When final, this guidance will represent FDA's current thinking on this topic.

[15] GDUFA III commitment letter at 46.

A controlled correspondence can be submitted by or on behalf of a generic drug manufacturer or related industry before ANDA submission. Under the GDUFA II commitment letter framework, correspondence seeking regulatory and/or scientific advice after issuance of a CRL or tentative approval, or after ANDA approval, was considered general correspondence. Under the GDUFA III commitment letter, these types of correspondence can be submitted as controlled correspondence. Also, under the GDUFA III commitment letter, a controlled correspondence can be submitted during an ANDA assessment cycle if an applicant seeks further feedback from FDA after a PSG Teleconference or seeks a Covered Product Authorization. During an ANDA assessment cycle, all other correspondence will be considered general correspondence and should be submitted to the ANDA so that it becomes part of the full administrative record for that application.

A. Guidance on Inquiries Within the Scope of Controlled Correspondence That Cannot Be Answered by FDA

1. Controlled Correspondence Related to a Pending Citizen Petition, Petition for Stay of Action, or Petition for Administrative Reconsideration of Action

If a controlled correspondence is submitted about an issue that relates to one or more pending citizen petitions, petitions for stay of action, or petitions for administrative reconsideration of action, FDA intends that the response to the controlled correspondence will explain that we cannot answer the question posed because the request is about an issue related to a petition and we will close the controlled correspondence.[16] Once FDA responds to the pending citizen petition, petition for stay of action, or petition for administrative reconsideration of action, the requestor can resubmit the controlled correspondence. Requestors can monitor the current status of the petition at https://www.regulations.gov.

2. Requests Related to Matters Still Under Consideration by the Agency

FDA occasionally receives requests for information about issues that the Agency is considering, but for which no scientific or regulatory decision has been made or for which there is no clear scientific consensus. For a request for which controlled correspondence is the appropriate pathway but the subject is still under consideration at the time of the goal date, FDA will notify the requestor that the goal date has been missed because the request raises issues about which FDA has not made a decision. In such instances, the request will remain open until FDA issues a response.

[16] Under the GDUFA I and GDUFA II commitment letters, if a controlled correspondence was submitted about an issue that related to one or more pending citizen petitions, petitions for stay of action, or petitions for administrative reconsideration of action, the time period for responding started on the date FDA responded to the petition (if there was only one petition) or the last pending petition.

B. Guidance on Inquiries Outside the Scope of Controlled Correspondence

1. Requests More Appropriately Addressed Through Other Mechanisms

In certain circumstances, controlled correspondence may not be the optimal mechanism to gain FDA's feedback on a topic. For example, topics that are general in nature would be more appropriately considered as part of the Regulatory Science Initiative, such as the proposed use of in vitro data to support demonstration of bioequivalence for a class of RLDs for which no ANDAs have been submitted.

As another example, for certain questions, it may be more appropriate to submit a meeting request in lieu of submitting a controlled correspondence. The purpose of the controlled correspondence process is to provide a mechanism for a direct inquiry about FDA's position with respect to a particular element of generic drug development and for the Agency's direct, brief, and timely response. A controlled correspondence may also be appropriate if the requestor has clarifying questions or questions that are outside of the scope of a meeting request. In contrast, one of the meetings described in the GDUFA III commitment letter may be a better forum in which to seek a dialogue with the Agency about a particular matter for which the controlled correspondence process is not suitable (e.g., methods of characterization for complex products or clinically critical BE considerations). FDA recommends that prospective applicants and applicants refer to the GDUFA III commitment letter and FDA's guidances for industry for additional information on GDUFA III meetings.[17] For such questions that are more appropriately addressed in a meeting, the Agency will notify the requestor of the recommended alternative pathway and close the controlled correspondence.

2. Exceptions to the Definition of Controlled Correspondence

Historically, FDA has excluded three types of inquiries about generic drug development from controlled correspondence: (1) requests for recommendations on the appropriate design of BE studies for a specific drug product; (2) requests for review of BE study protocols; and (3) requests for meetings to discuss generic drug development. Additional information on these types of inquiries is provided below.

First, FDA will continue to address PSG requests consistent with the public process described in the Agency's guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010) and FDA's good guidance practices regulation.[18] Under this approach, FDA publishes BE recommendations in PSGs. The availability of a PSG is announced in the *Federal Register*, and public comments are requested for a designated period to ensure they are received

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[17] See footnote 4. See, e.g., FDA's guidances for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Oct. 2022) and *Post Complete Response Letter Clarification Teleconferences Between FDA and ANDA Applicants Under GDUFA* (Oct. 2022).

[18] 21 CFR 10.115.

before the Agency begins work on the final version of the guidance. However, comments can be submitted on draft or final guidance documents at any time under our good guidance practices. The PSG process enhances transparency, provides a mechanism for public comment about recommended BE studies, provides for more efficient use of Agency resources, and follows FDA's good guidance practices regulation.

With this public process, FDA can be proactive in developing and publishing guidance for new drug products without waiting for inquiries about BE methodologies from individual requestors.[19] FDA anticipates that this process will continue to expedite the availability of BE methodologies to generic drug manufacturers. However, this process involves time frames that differ from the goal dates for controlled correspondence, and the Agency has determined that it would not be appropriate to circumvent this public process by responding to individual requestors to meet the GDUFA III commitment letter goal dates for controlled correspondence because we believe public input is important to the development of BE methodologies. The Agency will continue to consider BE guidance requests in prioritizing PSG development.[20]

Second, FDA will continue to generally exclude requests for BE study protocol review from controlled correspondence and the related goal dates.[21] These include requests for review of protocols for in vivo BE studies with pharmacokinetic, pharmacodynamic, or comparative clinical endpoints conducted to support demonstration of bioequivalence for a proposed generic drug. Historically, FDA has not considered such requests as controlled correspondence because

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[19] FDA has committed to continuing to issue PSGs identifying the methodology for generating evidence to support ANDA approval. For complex products approved in new drug applications (NDAs) on or after October 1, 2022, a PSG will be issued for 50 percent of such NDA products within 2 years after the date of approval, and for 75 percent of such NDA products, within 3 years after the date of approval. FDA will continue to develop PSGs for complex products approved before October 1, 2022, for which no PSG has been published. For non-complex drug products approved in NDAs on or after October 1, 2022, that contain a new chemical entity (as described in section 505(j)(5)(F)(ii) of the FD&C Act (21 U.S.C. 355(j)(5)(F)(ii))), a PSG will be issued within 2 years after the date of approval for 90 percent of such products. GDUFA III commitment letter at 23.

A complex product generally includes: (1) products with complex active ingredients (e.g., peptides, polymeric compounds, complex mixtures of active pharmaceutical ingredients, naturally sourced ingredients); complex formulations (e.g., liposomes, colloids); complex routes of delivery (e.g., locally acting drugs such as dermatological products, complex ophthalmological products, and otic dosage forms that are formulated as suspensions, emulsions, or gels); or complex dosage forms (e.g., transdermal systems, metered dose inhalers, extended release injectables); (2) complex drug-device combination products (e.g., prefilled auto-injector products, metered dose inhalers); and (3) other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement (GDUFA III commitment letter at 45-46).

[20] Interested parties can submit requests for a PSG to be developed through the CDER Direct NextGen Collaboration Portal, which can be accessed at https://edm.fda.gov/. In addition, interested parties, including those that fall outside the scope of entities that can submit controlled correspondence, can submit requests for consideration of alternative BE approaches to the public docket for PSGs (FDA-2007-D-0369).

[21] FDA intends to accept requests for BE study protocol review as controlled correspondence in two circumstances: (1) as part of a request for a Covered Product Authorization and (2) after issuance of a CRL that identified deficiencies related to establishing equivalence.

these requests are more time- and resource-intensive than other requests and often call for consultation with multiple disciplines within the Office of Generic Drugs (OGD), as well as with other offices or centers (e.g., the Center for Devices and Radiological Health). Below are recommended alternatives to submitting a request for BE study protocol review:[22]

- If the request is intended to address a specific question not covered by a PSG, FDA recommends submitting a controlled correspondence requesting FDA to comment on the specific question in lieu of submitting a request for BE study protocol review.

- If the request involves the evaluation of a BE study design that deviates from the BE study recommended in the PSG, FDA recommends submitting a controlled correspondence requesting that FDA evaluate the alternative approach in lieu of submitting a request for BE study protocol review.

- If the request involves multiple questions or complex issues, FDA recommends submitting a pre-ANDA meeting[23] request or a controlled correspondence in lieu of submitting a request for BE study protocol review.

Third, FDA will not treat requests for meetings as controlled correspondence, because, as described in section III.B.1 of this guidance, such requests serve a different purpose than controlled correspondence. In addition, meeting requests include different information from the requestor; materials and information submitted with a controlled correspondence should provide the Agency with the relevant information on which to base its considerations, while the materials submitted in support of a meeting request should help the Agency determine whether a meeting is appropriate. Accordingly, we will treat meeting requests separately.

3. Topics Outside the Scope of Controlled Correspondence

This section provides additional guidance on the types of inquiries that do not fall within the definition of *controlled correspondence*. First, during an ANDA assessment cycle, a controlled correspondence can only be submitted if an applicant seeks further feedback from FDA after a PSG Teleconference or to seek a Covered Product Authorization.[24] All other correspondence

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[22] Requestors that would like to submit a BE study protocol to FDA for review outside the controlled correspondence process should submit the protocol through the CDER Direct NextGen Collaboration Portal, which can be accessed at https://edm.fda.gov/.

[23] See FDA's guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Oct. 2022). We recommend applicants review the guidance and the GDUFA III commitment letter when evaluating whether the product under development could qualify for a pre-ANDA meeting.

[24] Consistent with FDA's historic practices, the Agency has identified limited situations, beyond those described in the GDUFA III commitment letter, in which we will consider a request for information in a controlled correspondence related to a specific pending ANDA. For example, the Agency will consider a request for

submitted during an ANDA assessment cycle will be considered general correspondence and should be submitted to the ANDA.

Second, inquiries submitted to FDA that are not directly related to generic drug development will not be considered controlled correspondence for the purposes of GDUFA III. For example, inquiries requesting information about the administrative practices of OGD, or about development of a generic drug for which there has never been a U.S.-approved RLD identified in FDA's *Approved Drug Products with Therapeutic Evaluations* (the Orange Book), will not be considered controlled correspondence.[25]

Third, as reflected in the definition of *controlled correspondence*, a controlled correspondence should not contain general questions related to product development. Consistent with FDA's past and current practices, general or insufficiently detailed questions related to product development are not appropriate subjects of controlled correspondence.[26] For example, an inquiry seeking information about general approval standards for a particular product is not an appropriate subject of a controlled correspondence. Likewise, an inquiry about the acceptability of an inactive ingredient without providing the proposed level of the inactive ingredient and information about the RLD, including a specific product strength for the RLD, provides insufficient detail for the Agency to respond. FDA provides information to stakeholders about its approval standards and general submission recommendations through FDA regulations and guidances, and the Agency encourages generic drug manufacturers and related industry to review this information before submitting controlled correspondence to OGD. The controlled correspondence process is intended to facilitate, not supplant, the generic drug development endeavor and the full scientific assessment of an ANDA.

4. Entities Outside the Scope of Controlled Correspondence

The controlled correspondence process is available to generic drug manufacturers and related industry, or their authorized representatives, that have a question related to a potential or actual ANDA submission to OGD, because this mechanism exists to facilitate generic drug development. Other parties (e.g., private citizens, financial firms, or public advocacy groups that

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information in a controlled correspondence regarding development of a new strength for a product for which the submitter is an applicant of a pending ANDA for other strengths. In addition, the Agency will consider a request for information in a controlled correspondence regarding development of a different package configuration for a product for which the submitter is an applicant of a pending ANDA for other package configurations. For example, if an inquiry pertaining to a gel in a metered-dose pump is submitted and there is a pending ANDA for gel in a unit-dose package, the controlled correspondence could still be accepted for review.

[25] Requestors can submit a controlled correspondence asking a question about an approved suitability petition and should provide the docket number for the approved suitability petition because that information is used to confirm that FDA can accept the controlled correspondence for review.

[26] Controlled correspondence should not be used to ask FDA to develop a new regulatory policy or to change an existing policy. However, FDA intends to monitor subjects of controlled correspondence to consider future topics for developing guidance documents.

are not directly involved in developing generic drugs) should submit their inquiries related to generic drugs to the Division of Drug Information.[27]

IV. SUBMITTING A CONTROLLED CORRESPONDENCE

A. How To Submit a Controlled Correspondence

Requestors seeking FDA's response to a controlled correspondence should submit the correspondence electronically through the CDER Direct NextGen Collaboration Portal (the portal), which can be accessed at https://edm.fda.gov.[28] This process will facilitate prompt consideration of and response to the controlled correspondence by the appropriate discipline based on assessment timelines identified in the GDUFA III commitment letter. Requestors should register a corporate email address with the portal.[29] We do not intend to consider portal submissions that are generated from general, personal accounts as controlled correspondence. If a requestor would like to obtain a secure email account, the requestor (or its U.S. agent) can apply for a secure email pathway by contacting secureemail@fda.hhs.gov.

FDA strongly discourages submitting controlled correspondence to individual FDA employees and submitting additional copies of a controlled correspondence in paper form, by courier, or by facsimile. As described in section V.A of this guidance, FDA intends to provide requestors notification via the portal on the status of a request soon after it is submitted, which should provide a requestor adequate assurance that the Agency has received the communication. The Agency's response will either state that FDA is considering the request as a controlled correspondence or provide the basis for not responding to it as a controlled correspondence, as described in this guidance.

B. Content of a Controlled Correspondence

[27] See contact information for the Division of Drug Information on the second title page of this guidance.

[28] Requestors that are unable to submit a controlled correspondence through the portal can send their controlled correspondence, as an attachment to an email, to GenericDrugs@fda.hhs.gov. In this situation, requestors should include the information specified in section IV.B of this guidance. GenericDrugs@fda.hhs.gov is a general OGD address to which certain submissions related to generic drugs can be submitted. If requestors submit their controlled correspondence to GenericDrugs@fda.hhs.gov instead of the portal, all communications regarding that controlled correspondence will be through email and will not be captured in the portal.

[29] Requestors can register with the portal at https://edm.fda.gov.

FDA recommends the cover letter[30] to a controlled correspondence be submitted on corporate letterhead, be dated within 7 calendar days of submission of the controlled correspondence, and include the following information:

- Name, title, address, email, phone number, and entity (e.g., corporate affiliation) of the person submitting the controlled correspondence. If the controlled correspondence is not submitted by the generic drug manufacturer or related industry's authorized representative, the generic drug manufacturer or related industry's authorized agent, or the agent's authorized representative, located in the United States, then FDA will not treat the submission as controlled correspondence under the GDUFA III commitment letter.[31]

  - If an authorized agent is submitting the controlled correspondence, identify the company for which you are the authorized agent and include a copy of a letter of authorization with each controlled correspondence.[32] The letter of authorization should be on corporate letterhead and dated within 1 year of the date the controlled correspondence is submitted. FDA intends to provide a response to the company's U.S. authorized agent or the agent's authorized representative, similar to FDA's practice when an ANDA is submitted.

- FDA-assigned controlled correspondence number and submission date of any previous, related controlled correspondence that was accepted for substantive review and response, if any, as well as a single copy of that previous controlled correspondence and FDA's response, if any.

  - For controlled correspondence regarding a CRL, FDA recommends submitting a copy of the CRL and identifying any other controlled correspondence or meeting requests related to that CRL.

- Relevant RLD(s) and/or reference standard(s),[33] as applicable, including application number, proprietary (brand) name, manufacturer, active ingredient, dosage form, route of administration, and strength(s).

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[30] For more information on preparing cover letters to controlled correspondence, see FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions* (Dec. 2021). When final, this guidance will represent FDA's current thinking on this topic.

[31] See the definition of *controlled correspondence* ("correspondence submitted to the Agency, by or on behalf of a generic drug manufacturer or related industry") (GDUFA III commitment letter at 46).

[32] A letter of authorization should be provided by all authorized agents, regardless of whether the prospective applicant or applicant is located in the United States.

[33] 21 CFR 314.3(b) ("*Reference standard* is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval").

- Statement that the controlled correspondence is related to either a potential ANDA submission to OGD, an ANDA that is pending with FDA, an ANDA that received a CRL and is pending with the applicant, an ANDA that received a tentative approval letter, or an approved ANDA.

  - Provide the ANDA number, including whether the controlled correspondence is related to a potential ANDA submission to OGD that has already received a pre-assigned ANDA number.

- Concise statement describing the controlled correspondence inquiry, including specific questions to be answered.

  - If the controlled correspondence is related to a deficiency identified in a CRL, include a reference to that specific deficiency.

- Recommendation for the appropriate FDA review discipline to assess the controlled correspondence. General information regarding review disciplines is provided in section IV.D of this guidance.

Requestors should also include, either in the cover letter or as an attachment to the cover letter, relevant prior research and supporting materials on the specific element of generic drug development about which the requestor seeks information. In addition, FDA recommends that all documents be dated.

If FDA determines that the inquiry does not contain the information specified in section IV.B of this guidance, then FDA will not consider the inquiry to be submitted as controlled correspondence for purposes of the GDUFA III commitment letter.

C. Additional Recommendations on the Content of Specific Types of Controlled Correspondence Inquiries

This section provides additional recommendations for the content of specific types of inquiries submitted as controlled correspondence.

1. Requests Related to Inactive Ingredients

The Agency often receives requests for information pertaining to whether particular inactive ingredients present at higher levels than the maximums listed in the Agency's Inactive Ingredient

Database (IID) are permissible in a generic drug.[34] FDA recommends that a requestor submit for evaluation no more than three inactive ingredients and no more than three proposed levels for a drug product in any given controlled correspondence. For example, in any given controlled correspondence:

- A requestor can submit (1) a request that proposes three inactive ingredients with one level each, or (2) a request that proposes one inactive ingredient with three levels.

- If the drug product is indicated for the adult and pediatric populations, a requestor can submit (1) a request that proposes one inactive ingredient with one level for three different dosing ranges (based on body weight or age range specified in the RLD labeling), or (2) a request that proposes three inactive ingredients with one level for one dosage range.

If the drug product is indicated for more than one route of administration, requests regarding inactive ingredients for each route of administration should be submitted in a separate controlled correspondence.

If a requestor submits a range of levels for an inactive ingredient, the Agency only intends to review the highest proposed level in that range for that inactive ingredient. In addition, requestors should only submit the inactive ingredients they wish to be evaluated and their proposed levels and not the whole formulation.

FDA notes that certain inactive ingredients are composed of multiple subcomponents (e.g., flavors). If levels of individual subcomponents are found within limits by the Agency when reviewed through a controlled correspondence, applicants should be aware that this does not necessarily mean the whole inactive ingredient will be found to be within acceptable limits during ANDA assessment. This is because the whole inactive ingredient's safety profile is evaluated in the context of the entire drug product formulation during ANDA assessment (and, as applicable, during assessment of the acceptability of the pertinent drug master file).

Furthermore, when a flavor and/or the subcomponents of a flavor are expressed as ≤ 0.1 percent (weight/weight) of the total weight of the drug product in a controlled correspondence, the Agency uses this 0.1 percent (weight/weight) limit as a threshold determination that the flavor and/or the subcomponents of a flavor are acceptable at the filing stage only. This is because the amount of a flavor and/or subcomponents of a flavor is reviewed by FDA during ANDA

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[34] The IID Update mailbox (IIDUpdate@fda.hhs.gov) can be used to inform FDA of errors in the IID and to ask questions about IID listings. The GSRS mailbox (FDA-GSRS@fda.hhs.gov) can be used for unique ingredient identifier requests and for questions about the preferred term for an excipient listed in the IID. These types of communications should not be sent to GenericDrugs@fda.hhs.gov. The IID is available at https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. For more information on the IID, see the draft guidance for industry *Using the Inactive Ingredient Database* (July 2019). When final, this guidance will represent the current thinking of FDA.

assessment when the complete drug product formulation information is available to assessors. Thus, the Agency's filing determination does not mean that the proposed amount will ultimately be found approvable at the ANDA assessment stage.

A requestor should wait for FDA's response to the controlled correspondence before submitting a different request for consideration. The Agency believes this is a reasonable limit based on what can be evaluated for a particular drug product within the GDUFA III commitment letter goal date time frame. This process also encourages requestors to provide targeted submissions to the Agency and allows requestors to refine their subsequent formulation proposals based on FDA's previous responses.

Such requests should identify the RLD (including the specific drug product strength(s)), the requestor's determination of the maximum daily dose of the drug product, 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). Absent that information, there is no means for FDA to evaluate the safe use of that inactive ingredient, which depends on many factors, including context of use (e.g., dose, route of administration, duration of use, and patient population) for the RLD. Although FDA may provide information regarding an inactive ingredient through a controlled correspondence, FDA evaluates the ultimate acceptability of an inactive ingredient in the context of a specific proposed drug product's formulation during ANDA assessment, when the Agency has the full complement of data and information in support of ANDA approval to consider.

2. Requests for Formulation Assessment (e.g., Q1/Q2 Sameness)

For certain types of products, FDA's regulations generally require that proposed products be qualitatively (Q1) and quantitatively (Q2) the same as the RLD with respect to certain inactive ingredients.[35] When submitting a controlled correspondence for a Q1/Q2 sameness assessment, FDA recommends the controlled correspondence include the information about the RLD in the bulleted list below, which can be found in the Orange Book. Consistent with the Agency's past and current practices, FDA does not intend to review proposed formulations for Q1/Q2 sameness that are not required to be Q1/Q2 the same as the RLD by regulation. Formulations that are not Q1/Q2 the same as the RLD are permissible for certain products as long as the differences do not affect the safety or effectiveness of the product. The acceptability of such differences would be considered in the context of ANDA assessment. It should be noted that Agency policy or regulation may limit the amount or type of information that FDA can disclose in response to a request for Q1/Q2 sameness assessment, and that FDA does not intend to provide clarification on why a formulation is not Q1/Q2 the same as the RLD (see section V.B of this guidance).[36]

[35] 21 CFR 314.94(a)(9)(iii-iv).

[36] See e.g., 21 CFR 20.61(a) and (b).

For products where Q1/Q2 sameness is not required by regulation, 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.[37] 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, and should include the information about the RLD and reference standard (if the reference standard is not the RLD) in the bulleted list below. Consistent with the Agency's past and current practices, FDA does not intend to review requests for formulation assessment that are not recommended as part of a BE approach in a guidance.[38] In addition, FDA only intends to opine as to whether it is acceptable for the applicant to use the requested BE approach based on the proposed formulation and does not intend to comment on whether the proposed formulation is the same (e.g., Q1/Q2) as the RLD or reference standard.

As described above, the following information should be included in the controlled correspondence:

- Application holder
- Application number
- Proprietary name
- Active ingredient
- Strength (if a parenteral drug product, specify both the total quantity of drug substance in the container closure and the concentration of the drug substance)
- If a parenteral drug product, specify the fill volume
- Dosage form
- Route of administration
- Approval date
- Marketing status (i.e., whether the product is prescription, over-the-counter, or in the "Discontinued" section of the Orange Book (which includes drug products that have been withdrawn from the market))

The formulation descriptions should include adequate details, including salt and hydration forms, purity, grade or type, function, and appropriate units (e.g., amount/milliliter, amount/gram,

[37] For more information on the terms *RLD* and *reference standard*, see the guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (Oct. 2020).

[38] If FDA has previously reviewed and responded to a proposed alternative BE approach within the scope of a pre-ANDA product development meeting, and FDA's response indicated that the proposed formulation is not appropriate for the proposed alternative approach, then the requestor can submit a controlled correspondence for feedback on the appropriateness of using the proposed alternative approach with an updated formulation.

492 percentage weight/weight, percentage weight/volume, percentage volume/volume), as
493 applicable, of the active ingredients and inactive ingredients in the product.[39]
494
495 FDA recommends that no more than three proposed formulations of a single drug product be
496 submitted in one controlled correspondence. Limiting a single controlled correspondence to no
497 more than three formulation assessment requests allows for FDA's targeted and timely review of
498 such requests. In addition, the Agency recommends against submitting a request for formulation
499 assessment and a separate request for evaluation of a proposed inactive ingredient amount or
500 concentration at the same time.
501
502 If a requestor is seeking formulation assessment for multiple drug products, FDA recommends
503 that each drug product request be submitted in a separate controlled correspondence. Thus, a
504 requestor should not seek formulation assessment for generic drugs with different RLDs in a
505 single controlled correspondence. This includes separate formulation assessment requests for
506 drug products with multiple strengths, such as parenteral drug products with different fill sizes,
507 because each strength is a separate drug product.[40]
508
509 *3. Requests Related to Product Quality*
510
511 In addition to product quality questions related to generic drug development, the Agency often
512 receives requests for information pertaining to chemistry, manufacturing, and controls for Type
513 II drug master files for drug substances submitted in support of generic drug applications. FDA
514 recommends that a requestor include prior research and supporting product quality information
515 in the controlled correspondence so the Agency can adequately respond to the inquiry. The level
516 of detail of the supporting product quality information should be appropriate considering the
517 question(s) being asked. Typically, a submission related to product quality would include, as
518 applicable, a brief description of the proposed formulation, manufacturing process, container-
519 closure system, and developmental studies. For example:

520 • An inquiry on stability bracketing/matrixing design should include whether a common
521 blend is used to make the drug product, proposed product strengths, storage conditions,
522 and a description of the container-closure system, including any other information to
523 justify the reduced stability design.

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[39] To facilitate consideration of the request, FDA recommends that the inactive ingredient and/or the formulation information be presented in the format in which it would be submitted in an ANDA. In cases in which a drug product is supplied as a dose pack, such as a vial containing lyophilized product and a diluent, the requestor should submit formulation compositions for both the lyophilized product and the diluent.

[40] For parenteral drug products, strength is generally determined by both the total quantity of drug substance in a container closure and the concentration of the drug substance. Orange Book, 42nd ed. (2022), at xvii; see also 80 FR 6802 at 6816 (February 6, 2015). Therefore, a deviation from the total drug content of the RLD parenteral drug product or the concentration would constitute a change in strength. The Orange Book Preface explains, however, that the "strengths of certain parenteral drug products, including contrast agents, may be expressed as a percentage" (Orange Book, 42nd ed. (2022), at xvii).

- A question on size, shape, or other physical attributes of a drug product should be supported by comparative data of the proposed generic drug and RLD with regard to product dimensions, volume, images, and other relevant properties.

A detailed description, with relevant prior research and supportive information, in a controlled correspondence will increase the likelihood that FDA will have sufficient information to provide a specific response to the inquiry. We also recommend that requestors review FDA's guidance for industry *Questions and Answers on Quality Related Controlled Correspondence* (September 2021) before submitting a controlled correspondence.

4. Requests Related to the Evaluation of the User Interface of a Drug-Device Combination Product

Requestors can submit controlled correspondence requesting preliminary feedback regarding differences between the user interface of a proposed generic drug-device combination product as compared to the user interface of its RLD. These submissions should include comparative analyses,[41] specific questions about the user interface for the proposed generic combination product, and three samples each of the proposed generic combination product and the RLD.[42] If the requestor would like FDA's feedback on more than one strength, the requestor should include three samples of each strength (proposed generic and RLD) unless the device user interfaces of the different strengths are identical except for color scheme and labeling information. In this case, three samples of one strength (proposed generic and RLD) and one sample of each of the other strengths are sufficient. If the samples of the generic combination product are prototypes and do not represent the final, to-be-marketed version, the controlled correspondence should specify that the samples are prototypes and identify any components (including device labeling) that have been omitted or are still in development. Questions related to device performance and specifications are considered product quality questions and should be submitted in a separate controlled correspondence (see section IV.C.3 of this guidance).

5. Requests Requiring Review by More Than One Discipline

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[41] For more information on how to conduct analyses of the proposed user interface for a generic drug-device combination product when compared to the user interface of the RLD, see FDA's draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan. 2017). When final, this guidance will represent FDA's current thinking on this topic.

[42] Product samples should be sent to:

Office of Research and Standards
Office of Generic Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Building 75, Room 4723
Silver Spring, MD 20993

If a requestor seeks information related to separate elements of generic drug development or postapproval submission requirements that require review by more than one discipline, which are identified in section IV.D of this guidance (e.g., information on a proposed formulation and proposed product labeling), FDA recommends that the requestor submit separate requests regarding the product.[43] This process will facilitate our timely review and response.

6. Considerations for Specific Types of Level 1 Controlled Correspondence

Below are additional recommendations regarding specific types of inquiries submitted as level 1 controlled correspondence.

a. Controlled correspondence submitted after a PSG teleconference

When a new or revised PSG is published and an applicant or prospective applicant has already commenced an in vivo BE study (i.e., the study protocol has been signed by the study sponsor and/or the contract research organization), the applicant or prospective applicant can request a PSG Teleconference to obtain FDA's feedback on the potential impact of the new or revised PSG on its development program.[44] If the applicant or prospective applicant seeks further feedback from FDA after the PSG Teleconference, they can request a Pre-Submission PSG Meeting or a Post-Submission PSG meeting, or they can submit a controlled correspondence.[45] FDA recommends that requestors do not submit a controlled correspondence and a request for a Pre-Submission PSG Meeting or a Post-Submission PSG meeting at the same time.[46]

b. Controlled correspondence submitted after issuance of a CRL or tentative approval

FDA intends to respond to controlled correspondence seeking regulatory and/or scientific advice after the issuance of a CRL for an ANDA and after the issuance of a CRL for a supplement as long as the CRL for the ANDA or supplement was issued on or after October 1, 2022. If the CRL was issued before October 1, 2022, the correspondence should be submitted as general correspondence. A controlled correspondence submitted after issuance of a CRL should not be used to submit proposed responses to deficiencies identified in the CRL to FDA for review.

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[43] Requests requiring review by more than one discipline can be submitted concurrently. As discussed in section IV.B of this guidance, FDA recommends that a controlled correspondence include the submission date of any other, related controlled correspondence that was accepted for substantive review and response.

[44] GDUFA III commitment letter at 24.

[45] Id.

[46] FDA may deny a Pre- or Post-Submission PSG Meeting if the inquiry would be more appropriately resolved through a controlled correspondence. FDA may grant a Pre- or Post-Submission PSG meeting after such a controlled correspondence if FDA determines that any issues remain unresolved or would be more appropriately resolved in a meeting (GDUFA III commitment letter at 25).

FDA will also respond to controlled correspondence submitted on or after October 1, 2022, after issuance of a tentative approval.

c. Requests submitted after ANDA approval and concerning postapproval submission requirements

FDA will respond to controlled correspondence submitted on or after October 1, 2022, that contains questions about a specific approved ANDA.[47] FDA will also respond to controlled correspondence submitted on or after October 1, 2022, seeking information on postapproval submission requirements that are not covered by CDER guidance on postapproval changes and are not specific to an ANDA (i.e., the requirements impact more than one ANDA owned by the application holder).[48] Such controlled correspondence includes, but is not limited to, specific questions related to a product site transfer and specific questions related to modernizing a manufacturing facility (e.g., expanding an existing production line or constructing a new building within an existing manufacturing facility) that impact more than one ANDA. FDA recommends submitting questions concerning postapproval submission requirements in a separate controlled correspondence from other questions (e.g., a question about post-approval manufacturing requirements should be submitted in a separate controlled correspondence from a question about a quality deficiency identified in a CRL).

7. Considerations for Level 2 Controlled Correspondence

Below are additional recommendations regarding inquiries submitted as level 2 controlled correspondence.

a. Requests that involve evaluation of clinical content

Consistent with FDA's past and current practices, FDA will continue to consider controlled correspondence that requires evaluation of clinical content (and is therefore level 2 controlled correspondence) to include requests that require input from OGD's Office of Safety and Clinical Evaluation and OGD's Office of Research and Standards Clinical Safety and Human Subject Research Team. As further described in section IV.C.7.d of this guidance, FDA will also consider controlled correspondence that requires input from other offices and centers outside of OGD (e.g., the Center for Devices and Radiological Health), including about the evaluation of clinical content, to be level 2 controlled correspondence. The evaluation of clinical content includes, but is not limited to, clear, specific questions related to the planning of a BE study with comparative clinical endpoints and questions related to adverse events that occur during the conduct of a BE study.

b. Requests for a Covered Product Authorization

[47] GDUFA III commitment letter at 11 and 46.

[48] GDUFA III commitment letter at 46.

FDA will consider requests for a Covered Product Authorization, including the review of BE protocols for development and testing that involve human clinical trials for an ANDA if the RLD is subject to a REMS with ETASU to be level 2 controlled correspondence.[49] FDA will also consider requests for a Covered Product Authorization to obtain sufficient quantities of an individual covered product subject to a REMS with ETASU to be level 2 controlled correspondence when development and testing does not involve clinical trials.[50]

FDA has issued guidance on how to obtain a Covered Product Authorization. This draft guidance for industry *How To Obtain a Covered Product Authorization* (Sep. 2022) explains how to submit a request for a CPA and what to include in the request.[51]

c. Requests for evaluation of alternative BE approaches

FDA will consider requests to evaluate alternative BE approaches (e.g., pharmacokinetic, in vitro, comparative clinical endpoints) for drug products for which a PSG is available to industry to be level 2 controlled correspondence. In addition, FDA will consider requests to use an alternate reference product in a BE study, or otherwise use an alternative BE approach, when there is no market availability of the reference standard and the RLD, and there are no approved generic drugs referencing the same listed drug, to be level 2 controlled correspondence.[52]

d. Requests that require input from another office or center

FDA will consider requests that require the review discipline to obtain input from another office or center to be level 2 controlled correspondence. For example, if OGD's Office of Research and Standards has to consult OGD's Office of Bioequivalence or OPQ's Office of Lifecycle Drug Products has to consult OPQ's Office of Biotechnology Products on a request, that would constitute a level 2 controlled correspondence. As another example, if the controlled correspondence includes questions about the device constituent part of a drug-device combination product, and those questions require input from another office (e.g., OGD's Office of Safety and Clinical Evaluation or the Office of Surveillance and Epidemiology) or center, then that would constitute a level 2 controlled correspondence. During substantive review of the

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[49] GDUFA commitment letter at 46.

[50] Id.

[51] When final, this guidance will represent FDA's current thinking on this topic.

[52] Section 505(j)(2)(A)(iv) of the FD&C Act requires ANDA applicants to include information showing that their proposed new drug is bioequivalent to a previously approved "listed drug." Listed drugs are those that have been approved for safety and effectiveness under section 505(c) of the FD&C Act or approved under section 505(j) of the FD&C Act (section 505(j)(7) of the FD&C Act; 21 CFR 314.3). Given the potential for bioequivalence inconsistencies that may result from differences between a non-U.S.-approved product and the U.S. RLD, the Agency generally does not accept bioequivalence studies based on a non-U.S.-approved product to show that a drug is bioequivalent to the U.S. RLD.

controlled correspondence, FDA might determine that input from another office or center is required and change the classification of the controlled correspondence from level 1 to level 2.

D. Controlled Correspondence Review Disciplines

This section provides additional information on the different disciplines that might review and respond to a controlled correspondence. In addition, this section provides examples of the types of inquiries each discipline reviews. The Agency anticipates that this information will assist requestors in recommending the appropriate discipline to review a particular controlled correspondence. These descriptions are not intended to be exhaustive, and FDA has the discretion to determine which discipline should review and respond to a controlled correspondence.

1. OGD's Office of Bioequivalence

The Office of Bioequivalence reviews correspondence containing inquiries related to the planning of BE studies. The Office of Bioequivalence also reviews questions related to the maximum daily exposure of an inactive ingredient. In addition, the Office of Bioequivalence reviews controlled correspondence when applicants want to add an additional strength to their approved product line and request feedback on whether they need to conduct the studies recommended in the PSG for the additional strength.

2. OGD's Office of Research and Standards

The Office of Research and Standards reviews correspondence about alternative BE approaches to those recommended in a PSG and questions related to the use of modeling and simulation methods. The Office of Research and Standards also reviews controlled correspondence submitted before ANDA submission that contains questions about complex products,[53] including questions on formulation sameness (e.g., Q1/Q2 sameness) for complex products. In addition, the Office of Research and Standards reviews questions submitted before ANDA submission about the user interface of drug-device combination products.

3. OGD's Office of Safety and Clinical Evaluation

The Office of Safety and Clinical Evaluation reviews correspondence containing questions on the maximum daily dose, thresholds for extractable and leachable studies, and requests for Covered Product Authorizations, including those involving review of BE protocols for development and testing that involves human clinical trials for drug products subject to a REMS with ETASU. The Office of Safety and Clinical Evaluation also reviews correspondence sent to the Agency after issuance of a CRL or after ANDA approval that contains questions on the user interface of a drug-device combination product.

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[53] See footnote 19 for the definition of *complex product*.

699
700 *4. OGD's Office of Regulatory Operations, Division of Filing Review*
701
702 The Division of Filing Review reviews correspondence containing inquiries regarding Q1/Q2
703 sameness and inquiries that involve the review of the amount per dosage unit or percent
704 composition of inactive ingredients by reference to the FDA's Inactive Ingredient Database.
705
706 *5. OGD's Office of Regulatory Operations, Division of Labeling Review*
707
708 The Division of Labeling Review reviews correspondence regarding submission requirements
709 when the ANDA packaging configuration differs from the RLD's and appropriate labeling
710 differences.
711
712 *6. OGD's Office of Generic Drug Policy*
713
714 The Office of Generic Drug Policy, which includes the Division of Orange Book Publication and
715 Regulatory Assessment, reviews correspondence regarding RLD designation or certain reference
716 standard selection questions.
717
718 *7. Office of Pharmaceutical Quality*
719
720 The Office of Pharmaceutical Quality (OPQ) reviews correspondence containing inquiries
721 regarding chemistry, manufacturing, and controls, including product quality microbiology for
722 generic drugs. In addition, OPQ reviews inquiries related to Type II drug master files for drug
723 substances submitted in support of generic drug applications.
724
725 As listed below, OPQ contains subdisciplines that respond to various types of controlled
726 correspondence:
727
728 - The Office of Lifecycle Drug Products responds to correspondence containing inquiries
729 related to formulation, specifications, container-closure, and stability.
730 - The Office of New Drug Products, Division of Lifecycle Active Pharmaceutical
731 Ingredient, responds to correspondence containing inquiries related to starting materials,
732 polymorphs, and drug substance manufacturing processes.
733 - The Office of New Drug Products, Division of Biopharmaceutics, responds to
734 correspondence containing inquiries related to dissolution testing, dissolution methods,
735 and in vitro-in vivo correlation.
736 - The Office of Pharmaceutical Manufacturing Assessment, Division of Microbiology
737 Assessment, responds to correspondence containing inquiries related to sterile
738 processing, bacterial endotoxin limits, and antimicrobial testing.
739 - The Office of Pharmaceutical Manufacturing Assessment, Division of Pharmaceutical
740 Manufacturing, responds to correspondence containing inquiries such as those related to
741 blend uniformity, excess fill volumes, facility information submission recommendations,
742 and current good manufacturing practice requirements.

Consistent with the recommendation in section IV.C.5 of this guidance, requestors with inquiries related to generic drug development or postapproval submission requirements for more than one OPQ subdiscipline should generally submit the inquiries for each specific subdiscipline in separate controlled correspondence to facilitate a timely and complete response, with the following exception: for controlled correspondence related to a CRL, requestors should submit inquiries for OPQ in a single controlled correspondence.

V. FDA'S COMMUNICATIONS TO REQUESTORS AND REQUESTS TO CLARIFY AMBIGUITIES IN FDA'S CONTROLLED CORRESPONDENCE RESPONSE

A. Communications Related to Initial Submissions

For inquiries submitted through the portal, FDA will provide the following information to a requestor through the portal regarding receipt and consideration of the inquiry.[54]

Upon receipt of a submission, FDA will evaluate whether the submission will be considered a controlled correspondence for the purposes of the GDUFA III commitment letter. FDA will then send the requestor one of two emails that can be accessed through the portal: (1) an email confirming acceptance of the submission as a controlled correspondence, which will include an FDA-assigned controlled correspondence number;[55] or (2) an email informing the requestor either that the Agency does not consider the submission a controlled correspondence and the basis for that decision or that FDA lacks adequate information to make this determination. In most instances, we anticipate confirming acceptance of the submission within 7 calendar days,[56] and the communication will contain a receipt date[57] that the requestor can use to calculate the goal date. If a requestor resubmits a request for information that addresses any problem that FDA identified with a previous request, the Agency will consider this to be a new controlled correspondence and process it as such.

If FDA determines, during substantive review of the inquiry, that the inquiry lacks sufficient information, it can either close the controlled correspondence at that time or contact the requestor for additional information through the portal. If the Agency decides to close the controlled

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[54] For inquiries submitted to GenericDrugs@fda.hhs.gov, FDA's communications regarding the controlled correspondence will be sent to the email address from which the controlled correspondence originated.

[55] OGD recommends that the requestor refer to the controlled correspondence using the FDA-assigned controlled correspondence number in the cover letter of any related ANDA submissions and include a copy of the correspondence.

[56] If you do not receive confirmation from FDA within 7 calendar days, please contact GenericDrugs@fda.hhs.gov.

[57] As noted above, FDA will calculate the goal date from the day after a submission (GDUFA III commitment letter at 4).

777 correspondence, it will notify the requestor through the portal of that decision and the basis for
778 that decision. If FDA contacts the requestor for additional information, the goal date for that
779 controlled correspondence will be extended by the amount of time that the Agency's request for
780 additional information is outstanding with the requestor.
781
782 After substantive review of the request for information in the controlled correspondence, FDA
783 will respond in written form via an email that can be accessed in the portal. FDA will only send
784 a response to the person who originally submitted the controlled correspondence. The length and
785 content of FDA's response will depend on the nature of the inquiry submitted. We intend that
786 the comments we provide in response to a controlled correspondence will be comprehensive as
787 of the date of the response. We note that comments in the response represent our thinking on a
788 topic at that time and that our thinking may evolve in the future.
789
790 FDA will not respond to status requests regarding pending controlled correspondence before the
791 goal date. If the Agency does not respond to the controlled correspondence by the goal date,
792 FDA will send an acknowledgement to the requestor with notification that the request is still
793 under consideration.
794
795 **B. Clarification of the Controlled Correspondence Response**
796
797 FDA will respond to requests to clarify ambiguities in the Agency's controlled correspondence
798 response, and such requests might be treated differently than follow-up questions. As defined in
799 the GDUFA III commitment letter, ambiguity in the controlled correspondence response "means
800 the controlled correspondence response or a critical portion of it merits further clarification."[58]
801 All requests for clarification of a controlled correspondence should be included in a single
802 submission to FDA. The request for clarification should be submitted within 7 calendar days of
803 issuance of FDA's controlled correspondence response.[59] Requests for clarification received
804 after 7 calendar days from issuance of the controlled correspondence response will be considered
805 a new controlled correspondence.
806
807 Requestors seeking clarification of ambiguities in FDA's controlled correspondence response
808 should submit the request electronically through the portal, which can be accessed at
809 https://edm.fda.gov.[60] The request should be submitted under the same event ID for the original

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[58] GDUFA III commitment letter at 45.

[59] The Agency believes that 7 calendar days provides a requestor sufficient time to review FDA's controlled correspondence response and identify any portion of the response the requestor believes is ambiguous. This process also ensures that requestors submit clarification requests for controlled correspondence that have recently been reviewed and responded to by the Agency.

[60] Requestors that are unable to submit a request for clarification through the portal can send their request, as an attachment to an email, to GenericDrugs@fda.hhs.gov. In this situation, requestors should include the information specified in section V.B of this guidance. For inquiries submitted to GenericDrugs@fda.hhs.gov, FDA's

controlled correspondence submission. The cover letter for the request to clarify ambiguities in the controlled correspondence response should include the following information:

- Name, title, address, email, phone number, and entity (e.g., corporate affiliation) of the person submitting the request for clarification. If the request for clarification is not submitted by the generic drug manufacturer or related industry's authorized representative, the generic drug manufacturer or related industry's authorized agent, or the agent's authorized representative, located in the United States, then FDA will not treat the request for clarification as subject to the GDUFA III commitment letter.

  - Where possible, the request for clarification should be submitted by the person who originally submitted the controlled correspondence on which clarification is sought. If this is not possible, FDA will accept the request from an alternate, authorized representative of the generic drug manufacturer or related industry, its authorized agent, or the agent's authorized representative, located in the United States.

  - If an authorized agent is submitting the request, identify the company for which you are the authorized agent and include a copy of a letter of authorization.[61] The letter of authorization should be on corporate letterhead and dated within 1 year of the date the request for clarification is submitted. FDA intends to provide a response to the company's U.S. authorized agent or the agent's authorized representative, similar to FDA's practice when an ANDA is submitted.

- FDA-assigned controlled correspondence number, submission date of the controlled correspondence on which the requestor is seeking clarification, a copy of that controlled correspondence, and FDA's response to the controlled correspondence.

- Clarifying questions and the corresponding section(s) of FDA's controlled correspondence response on which the requestor is seeking clarification.

The scope of the clarifying questions should be limited to the content of FDA's controlled correspondence response. Any requests to review follow-up questions, or new or additional information, will be considered a new controlled correspondence. In these instances, we recommend that the requestor submit a new controlled correspondence through the portal and include the FDA-assigned controlled correspondence number of the previous inquiry to facilitate FDA's review and response. This process ensures that the question is tracked and that all requestors are treated equitably.

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communications regarding the request for clarification will be sent to the email address from which the request originated.

[61] A letter of authorization should be provided by all authorized agents, regardless of whether the prospective applicant or applicant is located in the United States.

As agreed to in the GDUFA III commitment letter, FDA will review and respond to 90 percent of requests to clarify ambiguities in the controlled correspondence response within 21 calendar days of the Agency's receipt of the request.[62] If FDA determines that the request does not contain the information specified in the bulleted list in this section, the request will not be considered to be received for purposes of the GDUFA III commitment letter.

After reviewing the request for clarification, FDA, at its discretion, will either call the requestor or respond in written form via an email that can be accessed in the portal. FDA's response will either clarify the ambiguity in the controlled correspondence response or state that, in FDA's judgment, the controlled correspondence response does not merit further clarification. Any subsequent inquiries regarding FDA's response to a controlled correspondence or FDA's response to a request for clarification of ambiguities should be submitted in a new controlled correspondence.

[62] GDUFA III commitment letter at 11. FDA will calculate the goal date from the day after a submission (GDUFA III commitment letter at 4). For the purpose of meeting this commitment, requests to clarify ambiguities in FDA's controlled correspondence response will be received by the Agency Monday through Friday from 12:00 a.m. to 11:59 p.m. Eastern Standard Time/Eastern Daylight Time, excluding Federal holidays and days when the FDA office that will review the clarification request is closed.