
Controlled Correspondence Related to Generic Drug Development Guidance for Industry

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

**December 2020
Generics**

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Controlled Correspondence Related to Generic Drug Development Guidance for Industry¹

This guidance represents 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 office 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 replaces the September 2015 guidance for industry *Controlled Correspondence Related to Generic Drug Development*. The September 2015 guidance was issued as part of FDA's implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA I).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 the reauthorization of GDUFA (GDUFA II).³

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

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 Food and Drug Administration Safety and Innovation Act (Public Law 112-144).

³ FDA Reauthorization Act of 2017 (Public Law 115-52).

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II. BACKGROUND

GDUFA was reauthorized on August 18, 2017, to facilitate timely access to high-quality, affordable generic medicines.⁴ In accordance with the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter or GDUFA II Goals Letter)⁵ that accompanied the legislation, FDA agreed to certain goals and procedures for the review of controlled correspondence received both before and on or after October 1, 2017.⁶ Specifically, the Agency agreed that:

- FDA will review and respond to 90 percent of standard controlled correspondence within 60 calendar days of the date of submission.
- FDA will review and respond to 90 percent of complex controlled correspondence 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 14 calendar days of FDA's receipt of the request.⁷

In the case of controlled correspondence that raises an issue that relates to one or more pending citizen petitions, the 60- or 120-calendar day time period starts on the date FDA responds to the petition (if there is only one petition) or last pending petition.⁸

The GDUFA II Commitment Letter defined *standard controlled correspondence* as:

1. Correspondence submitted to the Agency, by or on behalf of a generic drug manufacturer or related industry, requesting information on a specific element of generic drug product development, as described in the September 2015 guidance for industry *Controlled Correspondence Related to Generic Drug Development*⁹

⁴ Id.

⁵ Available at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>.

⁶ The application of GDUFA II goals to controlled correspondence that was submitted during GDUFA I will be discussed in section III.C. of this guidance.

⁷ GDUFA II Commitment Letter at 9.

⁸ Id. As discussed in section III.A.1. of this guidance, this GDUFA II commitment also applies to controlled correspondence related to petitions for stay of action and petitions for administrative reconsideration of action.

⁹ Since this guidance replaces the September 2015 guidance for industry *Controlled Correspondence Related to Generic Drug Development*, FDA is incorporating the definition of controlled correspondence into this guidance.

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2. Concerning postapproval submission requirements that are not covered by guidance on postapproval changes and are not specific to an abbreviated new drug application (ANDA)¹⁰

The GDUFA II Commitment Letter defined *complex controlled correspondence* as correspondence involving:

1. Evaluation of clinical content
2. Review of bioequivalence (BE) protocols for drugs that reference listed drugs with risk evaluation and mitigation strategies (REMS) with elements to assure safe use (ETASU)
3. Requested evaluations of alternative BE approaches within the same study type (e.g., pharmacokinetic, in vitro, clinical)¹¹

This guidance provides additional detail and recommendations concerning:

- What inquiries FDA considers to be controlled correspondence for the purposes of meeting the Agency's GDUFA II commitment
- 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 response and the Agency's process for responding to those requests

III. CONTROLLED CORRESPONDENCE

Standard controlled correspondence and complex controlled correspondence are defined in the GDUFA II Commitment Letter and in section II of this guidance.

A. Guidance on Inquiries Within the Scope of Controlled Correspondence

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

¹⁰ GDUFA II Commitment Letter at 27-28.

¹¹ Id. at 25.

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Consistent with GDUFA I and FDA's current practice, if a controlled correspondence is submitted that raises an issue that relates to one or more pending citizen petitions, petitions for stay of action, or petitions for administrative reconsideration of action, the 60- or 120-day time period starts on the date FDA responds to the petition (if there is only one petition) or the last pending petition.¹² FDA will notify the requestor if the Agency determines that the controlled correspondence is related to an issue raised in a pending petition. When the Agency issues a response to the petition, it will commence consideration of the controlled correspondence. FDA will not notify the requestor when review of the controlled correspondence has commenced; the requestor 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 on issues that the Agency is considering, but for which no scientific or regulatory decision has been made or for which there is no clear clinical consensus. For a request for which controlled correspondence is the appropriate pathway but the subject is still under consideration at the time of the response 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.

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, a pre-ANDA meeting¹³ may provide a better forum in which to discuss certain issues, such as methods of characterization for complex products or clinically critical BE considerations. Other 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 BE for a class of reference listed drug (RLD) products for which no ANDAs have been submitted. For such questions, the Agency will notify the requestor of the recommended alternative pathway and close the control.¹⁴

¹² Id. at 9. FDA considers a controlled correspondence to be related to one or more pending petitions if we determine that a decision regarding the issue raised in the petition could affect our response to the controlled correspondence.

¹³ The pre-ANDA meetings referenced in the GDUFA II Commitment Letter only apply to meeting requests for complex products that may be submitted in an ANDA on or after October 1, 2017. FDA has received, responded to, and granted certain pre-ANDA meeting requests for products that do not fit within the definition of a complex product as defined in the GDUFA II Commitment Letter. Meeting requests for products that are not classified as complex products will be granted based on the workload and availability of staff and anticipated value to the ANDA assessment process.

¹⁴ Controlled correspondence is intended to request information on a specific element of generic drug development, so it is not appropriate for requests that ask FDA to develop a new regulatory policy or change an existing policy. As described elsewhere in this document, however, FDA intends to monitor subjects of controlled correspondence to consider future topics for developing guidance documents.

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2. Exceptions to the Definition of Controlled Correspondence

Historically, FDA has treated three types of inquiries that fall within the above definition of *controlled correspondence* differently from other inquiries on generic drug development: (1) requests for recommendations on the appropriate design of BE studies for a specific drug product (BE guidance requests); (2) requests for review of BE clinical protocols (clinical protocol requests); and (3) requests for meetings to discuss generic drug development before ANDA submission (pre-ANDA meeting requests). FDA's process to respond to these inquiries, as outlined in the GDUFA II Commitment Letter, is described further below.

First, FDA will continue to address BE guidance requests consistent with the public process described in the Agency's guidance for industry on *Bioequivalence Recommendations for Specific Products*¹⁵ and FDA's good guidance practices regulation.¹⁶ Under this approach, FDA publishes BE recommendations in product-specific guidances, the availability of which is announced in the *Federal Register*; public comments are requested for a designated period to ensure they are received before the Agency issues a final guidance, however, comments can be submitted on draft or final guidance documents at any time under our good guidance practices. The product-specific guidance process enhances transparency, provides a mechanism for public comment on 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 on BE methodologies from individual requestors.¹⁷ FDA anticipates that this process will continue to expedite the availability of BE methodologies to generic drug manufacturers. This process involves time frames that differ from the goal dates for controlled correspondence, however, 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 II goal dates for controlled correspondence because we believe public input is important

¹⁵ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹⁶ 21 CFR 10.115.

¹⁷ FDA has committed to issuing product-specific guidance identifying the methodology for developing drugs and generating evidence needed to support ANDA approval for 90 percent of new chemical entity new drug applications that are approved on or after October 1, 2017, at least 2 years before the earliest lawful ANDA filing date. However, this goal does not apply to complex products. (GDUFA II Commitment Letter at 14.) 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 and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions, or gels) or complex dosage forms (e.g., transdermals, metered dose inhalers, extended release injectables); (2) complex drug-device combination products (e.g., auto injectors, 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 II Commitment Letter at 25.)

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to the development of BE methodologies. The Agency will continue to consider BE guidance requests in prioritizing BE guidance development.¹⁸

Second, FDA will continue to exclude requests for BE clinical protocol review from controlled correspondence and the related goal dates if the RLD product is not subject to REMS ETASU. These requests include requests for review of protocols for in vivo BE studies with pharmacokinetic, pharmacodynamic, or comparative clinical endpoint studies conducted to support demonstration of BE for a proposed generic product. Historically, FDA has not considered such requests as controlled correspondence because 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 clinical protocol review:

- If the request for BE clinical protocol review is intended to address a specific question not covered by a product-specific BE guidance, FDA recommends that in lieu of submitting a request for BE clinical protocol review, parties submit a controlled correspondence requesting FDA to comment on the specific question.
- If the request for BE clinical protocol review involves the evaluation of a BE study design that deviates from the BE studies recommended in the available product-specific guidance, FDA recommends that in lieu of submitting a request for BE clinical protocol review, parties submit a controlled correspondence requesting FDA evaluate the alternative approach.
- If the request for BE clinical protocol review involves multiple questions or complex issues, FDA recommends that in lieu of submitting a request for BE clinical protocol review, parties submit a pre-ANDA meeting¹⁹ request or a controlled correspondence.

Third, FDA will not treat pre-ANDA meeting requests as controlled correspondence because such requests serve a different purpose than controlled correspondence and should include different information from the requestor. The purpose of the controlled correspondence process is to provide a mechanism for a direct inquiry on FDA's position with respect to a particular element of generic drug development and for the Agency's direct, brief, and timely response. The purpose of a pre-ANDA meeting request, by contrast, is to seek a dialogue with the Agency

¹⁸ Interested parties may submit requests for consideration of BE methods that modify or deviate from those proposed for a specific product to the public docket for product-specific BE guidances (FDA-2007-D-0369). As an alternative, generic drug manufacturers and related industry or their authorized representatives can submit controlled correspondence through the CDER Direct NextGen Collaboration Portal (the portal) requesting the evaluation of an alternative BE approach within the same study type for a drug product for which a product-specific BE guidance is available to industry (see section IV.C.6.). In addition, if a requestor wants clarification on a BE study recommended in the related product-specific guidance to support development of a generic drug product, the requestor can submit an inquiry as a controlled correspondence.

¹⁹ We remind applicants to review the GDUFA II Commitment Letter to determine whether the product under development meets the criteria as a complex product and may, therefore, follow the pre-ANDA development program outlined in the GDUFA II Commitment Letter.

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on 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). Similarly, 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 pre-ANDA meeting requests separately.

We recommend that parties submit requests for recommendations on the appropriate design of BE studies for a specific drug product and for review of BE clinical protocols through the CDER Direct NextGen Collaboration Portal (the portal), which can be accessed at <https://edm.fda.gov>. For meeting requests, parties should refer to the draft guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* regarding the process for submitting requests for meetings to discuss generic drug development before ANDA submission.²⁰

3. Topics Outside the Scope of Controlled Correspondence

This section provides additional guidance on the types of inquiries or topics that do not fall within the definition of standard or complex controlled correspondence described above. First, the Agency considers any question related to a specific pending or approved ANDA to be outside the scope of a controlled correspondence.²¹ Such inquiries should be submitted only to the ANDA so they can be included as part of the full administrative record for that application.

Second, inquiries that are submitted to FDA that are not directly related to generic drug development will not be considered controlled correspondence for the purposes of GDUFA II. For example, inquiries requesting information on the administrative practices of OGD, or on development of generic products 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.

Third, as reflected in the definition of controlled correspondence, FDA expects that a controlled correspondence will contain inquiries on a specific element of generic drug development or postapproval submission requirements and not general questions related to product planning. Consistent with FDA's past and current practices, general or insufficiently detailed questions related to product development are not the appropriate subject of controlled correspondence. For example, an inquiry seeking information on general approval standards for a particular product is

²⁰ When final, this guidance will represent FDA's current thinking on this topic.

²¹ The Agency has identified limited situations in which we will consider a request for information in a controlled correspondence related to a specific pending or approved ANDA. For example, the Agency will consider a request for information in a controlled correspondence regarding development of a new strength for a product for which the submitter is an applicant of a pending or approved ANDA for other strengths. The Agency also 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 or approved 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 or approved ANDA for gel in a unit-dose package, the controlled correspondence could still be accepted for review.

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not the appropriate subject of a controlled correspondence for the purposes of GDUFA II. Likewise, an inquiry about the acceptability of an excipient without a proposed level for a specific RLD (which includes a specific product strength) or a question about the general acceptability of a particular device provides insufficient detail for the Agency to respond. FDA provides information to stakeholders on 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.

4. Entities Outside the Scope of Controlled Correspondence

The controlled correspondence process, historically (and under the definition above), is available to generic drug manufacturers and related industry or their authorized representatives that have a question related to a potential 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 are not directly involved in developing generic drug products) should submit their inquiries related to generic drugs to the Division of Drug Information.²²

C. Application of GDUFA II Program Enhancements to Controlled Correspondence Submitted During GDUFA I

As stated in the GDUFA II Commitment Letter, FDA will “[c]ontinue to review and act on . . . controlled correspondence submitted prior to October 1, 2017, that have been assigned GDUFA I goal dates pursuant to the GDUFA I review metrics applicable to those submissions.”²³ For any controlled correspondence submitted during GDUFA I for which FDA issued a response after October 1, 2017, and for which a submitter requests clarification of ambiguities in the controlled correspondence response (see section V.B. below), FDA will grant such a request for clarification, when possible, within the performance goal identified in the GDUFA II Commitment Letter.²⁴

IV. SUBMITTING A CONTROLLED CORRESPONDENCE

A. How To Submit a Controlled Correspondence

Requestors seeking FDA’s response to a controlled correspondence by the goal dates articulated in the GDUFA II Commitment Letter (and listed above) should submit the correspondence

²² See contact information for the Division of Drug Information on the second title page of this guidance.

²³ GDUFA II Commitment Letter at 9-10. To “act on an application” means that FDA will either issue a complete response letter, an approval letter, a tentative approval letter, or a refuse to receive letter.

²⁴ See GDUFA II Commitment Letter at 9.

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electronically through the the portal, which can be accessed at <https://edm.fda.gov>.²⁵ This will facilitate prompt consideration of and response to the controlled correspondence by the appropriate discipline. Requestors should register a corporate email address with the portal.²⁶ 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, a requestor (or its U.S. agent) may apply for a secure email pathway by contacting secureemail@fda.hhs.gov.

FDA strongly discourages submitting controlled correspondence inquiries 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. below, 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

FDA recommends the cover letter to a controlled correspondence be submitted on corporate letterhead 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 II commitment letter.²⁷
- Please identify the company for which you are the authorized agent and include a copy of a letter of authorization with each controlled correspondence.²⁸ The letter of authorization should be on corporate letterhead and dated within one year of

²⁵ Requestors that are unable to submit a controlled correspondence through the portal may 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 may 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.

²⁶ Requestors may register with the portal at <https://edm.fda.gov>.

²⁷ See the definition of controlled correspondence (“A correspondence submitted to the Agency, by or on behalf of a generic drug manufacturer or related industry, requesting information on a specific element of generic drug product development”).

²⁸ When possible, FDA recommends identification of the applicant of the potential ANDA, which facilitates linkage of the controlled correspondence to the ANDA when submitted.

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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 practice when an ANDA is submitted.

- FDA-assigned control number and submission date of any previous, related controlled correspondence that was accepted for substantive review and response, if any, as well as a copy of that previous controlled correspondence and FDA's response, if any.
- Relevant RLD(s) and/or reference standard(s),²⁹ as applicable, including application number, proprietary (brand) name, manufacturer, active ingredient, dosage form, and strength(s).
- Statement that the controlled correspondence is related to a potential ANDA submission to OGD or a request concerning postapproval submission requirements. Include the ANDA number if the controlled correspondence is related to a submitted ANDA,³⁰ including an ANDA that FDA has refused to receive, or if the controlled correspondence is related to a potential and not yet submitted ANDA that has already been assigned an ANDA number.
- Concise statement of the inquiry for which the controlled correspondence is being submitted.
- Recommendation of the appropriate FDA review discipline to review the controlled correspondence. General information regarding review disciplines is provided in section IV.D. below.

Requestors also should 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.

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 GDUFA II.³¹

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

²⁹ 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").

³⁰ Although the Agency considers any question related to a specific pending or approved ANDA a review issue that should be submitted only to the ANDA, the Agency has identified requests for information related to a specific pending or approved ANDA that may be submitted in a controlled correspondence. See section III.B.3, note 21.

³¹ See section V.A. of this guidance for additional information.

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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 are permissible in a generic drug product.³² 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 may 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 a requestor submits a range of levels for an inactive ingredient, the Agency only will 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, not the whole formulation as this would include inactive ingredients that are not in question.

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 II goal date period. This also encourages applicants to provide targeted submissions to the Agency and allows applicants 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)) to allow FDA to evaluate the potential acceptability of an excipient in the context of a specific proposed drug product. Absent that information, there is no means for FDA to evaluate the safe use of that inactive ingredient, which depends on many factors, including the conditions of use (e.g., the indicated population including pediatrics, route of administration, and duration of use) 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 formulation during ANDA review, when the Agency has the full complement of data and information in support of ANDA approval to consider.

2. Requests for Q1/Q2 Formulation Assessment

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 inactive ingredients.³³ In addition, FDA's guidances sometimes recommend certain BE studies for drug

³² Parties seeking to provide information to update FDA's Inactive Ingredient Database (e.g., to correct information on FDA-approved products contained in the database or to provide data for FDA-approved products not in the database) should send such notifications to IIDUpdate@fda.hhs.gov. Such updates should not be submitted to GenericDrugs@fda.hhs.gov. The Inactive Ingredient Database is available at the FDA web page, <https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>.

³³ See e.g., 21 CFR 314.94(a)(9)(iii).

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products that are Q1/Q2 with respect to the RLD. When seeking review of proposed Q1/Q2 formulations, we recommend the controlled correspondence include the following information about the RLD (which can be found in the Orange Book):

- Relevant RLD application holder
- Application number
- Proprietary name
- Active ingredient
- Dosage form
- Route of administration
- RLD approval date
- Market status (i.e., whether the product is prescription, over-the-counter, or in the “Discontinued” section of the Orange Book, which lists 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, and function of the active ingredients and excipients.³⁴ FDA recommends that no more than three proposed Q1/Q2 formulations of a single drug product be submitted in one controlled correspondence. Limiting a single controlled correspondence to no more than three formulation requests allows for FDA’s targeted and timely review of such requests. In addition, the Agency recommends against submitting a request for a Q1/Q2 formulation assessment and a separate request for evaluation of a proposed inactive ingredient amount or concentration at the same time.

If a requestor is seeking formulation assessment for multiple drug products, FDA recommends that each drug product request be submitted in a separate controlled correspondence. Thus, a requestor should not seek Q1/Q2 formulation assessment for generic drugs with different RLDs in a single controlled correspondence. This also includes separate formulation assessment requests for drug products with multiple strengths, because each strength is a separate drug product. It should be noted that Agency policy or regulation may limit the amount or type of information that FDA may disclose in response to a request for Q1/Q2 formulation assessment.³⁵

Consistent with the Agency’s past and current practices, FDA does not intend to review proposed formulations that are neither required by regulation nor recommended in guidance to be Q1/Q2 to the RLD. Non-Q1/Q2 formulations are permissible for certain products so 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 an ANDA review. FDA also does not intend to provide clarification on why a formulation is not Q1/Q2 (see section V.B. below).³⁶

³⁴ 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.

³⁵ See e.g., 21 CFR 20.61(a) and (b).

³⁶ *Id.*

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3. Requests Related to Product Quality

The Agency often receives requests for information pertaining to chemistry, manufacturing, and controls for generic drugs and inquiries related to Type II drug master files for drug substances submitted in support of generic drug applications. FDA recommends that a requestor include prior research and supporting product quality information in the controlled correspondence, so the Agency can adequately respond to the inquiry. The level of detail of the supporting product quality information should be commensurate with the question(s) being asked. Typically, a submission related to product quality would include, as applicable, a brief description of the proposed formulation, manufacturing process, container-closure system, and developmental studies. For example: (1) an inquiry on stability bracketing/matrixing design should include whether a common blend is used to make the drug product, proposed product strengths, storage conditions, and a description of the container-closure system, including any other necessary information to justify the reduced stability design; and (2) a question on size, shape, or other physical attributes of a drug product should be supported by comparative data of the proposed generic drug product 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 the necessary information to provide a specific response to the inquiry.

4. Requests Requiring Review by More Than One Discipline

If a requestor seeks information related to separate elements of generic drug product development requiring review by more than one discipline (e.g., information on a proposed formulation and proposed product labeling), FDA recommends that the requestor submit separate requests regarding the product.³⁷ This will facilitate timely review and response.

5. Requests Concerning Postapproval Submission Requirements

As indicated in the definition of standard controlled correspondence, FDA will respond to controlled correspondence seeking information on postapproval submission requirements.³⁸ FDA will only respond to correspondence requesting information on postapproval submission requirements that are not covered by existing guidance on postapproval changes.³⁹ If the request is related to a specific ANDA, then FDA will not treat the request as controlled correspondence for purposes of GDUFA II.⁴⁰ Postapproval controlled correspondence includes, but is not

³⁷ Requests requiring review by more than one discipline may be submitted concurrently. As discussed in section IV.B., FDA recommends that a controlled correspondence include the submission date of any other, related controlled correspondence that was accepted for substantive review and response.

³⁸ GDUFA II Commitment Letter at 27-28.

³⁹ Guidances on postapproval changes include, but are not limited to, *Changes to an Approved NDA or ANDA Questions and Answers*. We encourage requestors to review all guidances on postapproval changes at the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁴⁰ GDUFA II Commitment Letter at 27-28. As discussed in section III.B.3. of this guidance, requests related to a specific ANDA should be submitted to the application.

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limited to, specific questions related to a product site transfer that would affect more than one approved ANDA and specific questions related to modernizing a manufacturing facility that is approved for more than one ANDA.

6. Complex Controlled Correspondence

Pursuant to the GDUFA II Commitment Letter, the definition of complex controlled correspondence includes controlled correspondence involving evaluation of clinical content, BE protocols for RLDs with REMS ETASU, and requested evaluations of alternative BE approaches within the same study type (e.g., pharmacokinetic, in vitro, clinical).⁴¹

Consistent with FDA's past and current practices, FDA will continue to consider controlled correspondence that requires evaluation of clinical content to include requests that require input from the Division of Clinical Review in OGD. FDA also will consider, on a case-by-case basis, whether controlled correspondence that requires input from other offices and centers (e.g., the Center for Devices and Radiological Health) includes the evaluation of clinical content and is therefore considered complex controlled correspondence by the Agency. The evaluation of clinical content also includes, but is not limited to, clear, concrete questions related to the planning of a BE study with clinical endpoints and questions related to adverse events that occur during the conduct of a BE study.

FDA will address requests for Covered Product Authorizations for RLDs subject to a REMS with ETASU as complex controlled correspondence, consistent with the timing requirements set forth in the law widely known as CREATES.⁴²

FDA will consider requests to evaluate alternative BE approaches within the same study type (e.g., pharmacokinetic, in vitro, clinical) to be complex controlled correspondence for drug products for which a product-specific BE guidance is available to industry.

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 might review. The Agency anticipates that this information will assist requestors in recommending the appropriate discipline to review a particular controlled

⁴¹ Id. at 25. FDA may determine that a controlled correspondence is a complex controlled correspondence at any point during our review of the inquiry. Please note that a complex controlled correspondence is defined by the content of the controlled correspondence and not whether the drug product is a complex product as defined in the GDUFA II Commitment Letter.

⁴² 21 U.S.C. 355-2. CREATES was enacted as part of the Further Consolidated Appropriations Act of 2020, and establishes a pathway to obtain samples of the RLD. For those who wish to use this pathway to obtain products subject to a REMS with ETASU, CREATES requires that the interested developer obtain a Covered Product Authorization from FDA and sets forth a 120-calendar day time period for FDA to review these requests; thus, these requests will be treated as complex controlled correspondence. The pathway for obtaining a Covered Product Authorization under CREATES replaces the process for obtaining a Safety Determination Letter described in the Agency's draft guidance for industry *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD*.

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correspondence, as suggested above in section IV.B. 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

FDA anticipates that the Office of Bioequivalence will review correspondence containing inquiries related to the planning of BE studies, including the review of protocols for drug products subject to REMS ETASU. The Office of Bioequivalence also will review questions related to the maximum daily exposure of an inactive ingredient.

2. OGD's Office of Research and Standards

FDA anticipates that the Office of Research and Standards will review correspondence containing questions on complex products⁴³ or drug-device combination products.

3. OGD's Office of Regulatory Operations, Division of Filing Review

FDA anticipates that the Division of Filing Review will review correspondence containing inquiries regarding FDA's Inactive Ingredient Database and drug product formulation.

4. OGD's Office of Regulatory Operations, Division of Labeling Review

FDA anticipates that the Division of Labeling Review will review correspondence regarding submission requirements when the ANDA packaging configuration differs from the RLD's and appropriate labeling differences.

5. OGD's Office of Generic Drug Policy

FDA anticipates that the Office of Generic Drug Policy, which includes the Orange Book staff, will review correspondence regarding patent listings or RLD designation or new reference standard selection questions.

6. Office of Pharmaceutical Quality, Office of Policy for Pharmaceutical Quality

FDA anticipates that the Office of Policy for Pharmaceutical Quality will coordinate the Office of Pharmaceutical Quality's (OPQ) review of correspondence among OPQ's Office of Lifecycle Drug Products, Office of New Drug Products/Division of Lifecycle API and Division of Biopharmaceutics, and Office of Process and Facilities, with input from the Office of Testing and Research and the OPQ Science staff as appropriate. OPQ will review correspondence containing inquiries regarding chemistry, manufacturing, and controls, as well as product quality microbiology for generic drugs. In addition, we anticipate that OPQ will review inquiries related to Type II drug master files for drug substances submitted in support of generic drug applications.

⁴³ See GDUFA II Commitment Letter at 25.

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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.⁴⁴

Upon receipt of a submission, FDA will evaluate whether the submission will be considered a controlled correspondence for the purposes of GDUFA II. 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 for the purposes of GDUFA II, which will include an FDA-assigned control number;⁴⁵ 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,⁴⁶ and the communication will contain a receipt date⁴⁷ 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 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 correspondence, it will notify the requestor through the portal of that decision and the basis for that decision. If FDA contacts the requestor for additional information, the GDUFA II goal date for that controlled correspondence will be extended by the amount of time that the Agency's request for additional information is outstanding with the requestor.

After substantive review of the request for information in the controlled correspondence, FDA will respond in written form via an email that can be accessed in the portal. FDA will only send

⁴⁴ 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.

⁴⁵ OGD recommends that the requestor refer to the controlled correspondence using the FDA-assigned control number in the cover letter of any related ANDA submissions and include a copy of the correspondence.

⁴⁶ If you do not receive confirmation from FDA within 7 calendar days, please contact GenericDrugs@fda.hhs.gov.

⁴⁷ Please refer to FDA's guidance for industry *Providing Regulatory Submissions in Electronic Format – Receipt Dates* 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.

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a response to the person who originally submitted the controlled correspondence. The length and content of FDA's response will depend on the nature of the inquiry submitted. We intend that the comments we provide in response to a controlled correspondence will be comprehensive as of the date of the response. We note that comments in the response represent our thinking on a topic at that time and that our thinking may evolve in the future.

FDA will not respond to status requests regarding pending controlled correspondence before the goal date.⁴⁸ If the Agency does not respond to the controlled correspondence by the goal date, FDA will send an acknowledgement to the requestor with notification that the request is still under consideration.⁴⁹

B. Clarification of the Controlled Correspondence Response

In general, FDA considers follow-up questions to FDA's controlled correspondence response and requests for additional information as new controlled correspondence. This ensures that the follow-up question is tracked and that all requestors are treated equitably. In these instances, we recommend that a requestor submit a new controlled correspondence and include the FDA-assigned control number of the previous inquiry to facilitate FDA's review and response.

FDA will respond to requests to clarify ambiguities in the Agency's controlled correspondence response, and such requests may be treated differently than follow-up questions. As defined in the GDUFA II Commitment Letter, ambiguity in the controlled correspondence response "means the controlled correspondence response or a critical portion of it, in FDA's judgment, merits further clarification."⁵⁰ All requests for clarification of a controlled correspondence should be included in a single submission to FDA. The request for clarification should be submitted within 7 calendar days of issuance of FDA's controlled correspondence response.⁵¹ Requests for clarification received after 7 calendar days from issuance of the controlled correspondence response will be considered a new controlled correspondence.

Requestors seeking clarification of ambiguities in FDA's controlled correspondence response should submit the request electronically through the portal, which can be accessed at <https://edm.fda.gov>.⁵² The cover letter for the request to clarify ambiguities in the controlled correspondence response should include the following information:

⁴⁸ For pre-FY 2015 controlled correspondence, OGD will strive to respond to these controls as expeditiously as practicable.

⁴⁹ In circumstances in which there is a related pending petition, FDA will not notify the requestor when review of the controlled correspondence has commenced and it is the responsibility of the requestor to monitor the current status of the petition at <https://www.regulations.gov> (see section III.A.1. of this guidance).

⁵⁰ GDUFA II Commitment Letter at 24.

⁵¹ 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. It also ensures that requestors submit clarification requests for controlled correspondence that have recently been reviewed and responded to by the Agency.

⁵² Requestors that are unable to submit a request for clarification through the portal may send their request, as an attachment to an email, to GenericDrugs@fda.hhs.gov. In this situation, requestors should include the information

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- Name, title, address, email, phone number, and entity (e.g., corporate affiliation) of the person submitting the request for clarification of the controlled correspondence response. If the request for clarification of FDA's controlled correspondence response 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, FDA will not treat the request for clarification as subject to the GDUFA II Commitment Letter.⁵³ Where possible, the request to clarify ambiguities in FDA's controlled correspondence response 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.
 - Please identify the company for which you are the authorized agent and include a copy of a letter of authorization. The letter of authorization should be on corporate letterhead and dated within one year of the date the request for clarification of FDA's controlled correspondence response 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 practice when an ANDA is submitted.
- FDA-assigned control number, submission date of the controlled correspondence on which the requestor is seeking clarification, a copy of that previous 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 new or additional information will be considered a new controlled correspondence and should be submitted as such to the portal.

As agreed to in the GDUFA II Commitment Letter, FDA will review and respond to 90 percent of requests to clarify ambiguities in the controlled correspondence response within 14 calendar days of the Agency's receipt of the request.⁵⁴ If FDA determines that the request does not

specified in section V.B. of this guidance. For inquiries submitted to GenericDrugs@fda.hhs.gov, FDA's communications regarding the request for clarification will be sent to the email address from which the request originated.

⁵³ Supra note 27.

⁵⁴ GDUFA II Commitment Letter at 9. 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.

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contain the information specified in the bulleted list in this section, the request will not be considered to be received for purposes of GDUFA II.

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.

VI. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average 5 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to the Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002.

<p>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0797 (expires 06/30/2023).</p>
