
Controlled Correspondence Related to Generic Drug Development Guidance for Industry

DRAFT GUIDANCE

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

**November 2017
Generics**

Contains Nonbinding Recommendations

Draft — Not for Implementation

Controlled Correspondence Related to Generic Drug Development Guidance for Industry

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**U.S. Department of Health and Human Services
Food and Drug Administration
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**November 2017
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**Controlled Correspondence Related to
Generic Drug Development
Guidance for Industry¹**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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.

When finalized, this guidance will replace the September 2015 guidance for industry *Controlled Correspondence Related to Generic Drug Development*.² The September 2015 guidance was issued as part of FDA's implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA I). This revised 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 I (GDUFA II).

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.

II. BACKGROUND

GDUFA II was signed into law on August 18, 2017 to facilitate timely access to high-quality, affordable generic medicines. In accordance with the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter or

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 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>.

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41 GDUFA II Goals Letter)³ that accompanied the legislation, FDA agreed to certain goals and
42 procedures for the review of controlled correspondence received both before and on or after
43 October 1, 2017.⁴ Specifically, the Agency agreed that:

- 44
- 45 • FDA will review and respond to 90 percent of standard controlled correspondence within
46 60 calendar days of the date of submission.
 - 47
 - 48 • FDA will review and respond to 90 percent of complex controlled correspondence within
49 120 calendar days of the date of submission.
 - 50
 - 51 • FDA will review and respond to 90 percent of submitter requests to clarify ambiguities in
52 the controlled correspondence response within 14 calendar days of FDA's receipt of the
53 request.⁵
 - 54

55 In the case of controlled correspondence that raises an issue that relates to one or more pending
56 citizen petitions, the 60- or 120-calendar day time period starts on the date FDA responds to the
57 petition (if there is only one petition) or last pending petition.⁶

58

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

- 60
- 61 1. Correspondence submitted to the Agency, by or on behalf of a generic drug
62 manufacturer or related industry, requesting information on a specific element of
63 generic drug product development, as described in the September 2015 guidance for
64 industry *Controlled Correspondence Related to Generic Drug Development*⁷
 - 65
 - 66 2. Concerning postapproval submission requirements that are not covered by guidance
67 on postapproval changes and are not specific to an abbreviated new drug application
68 (ANDA)⁸
 - 69

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

- 72
- 73 1. Evaluation of clinical content
 - 74
 - 75 2. Review of bioequivalence (BE) protocols for drugs that reference listed drugs with
76 risk evaluation and mitigation strategies (REMS) with elements to assure safe use
77 (ETASU)
 - 78

³ Available at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>.

⁴ 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.

⁵ GDUFA II Commitment Letter at 9.

⁶ Id.

⁷ Since this guidance, when finalized, will replace the September 2015 guidance for industry *Controlled Correspondence Related to Generic Drug Development*, FDA is incorporating the definition of controlled correspondence into this guidance.

⁸ GDUFA II Commitment Letter at 27-28.

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- 79 3. Requested evaluations of alternative BE approaches within the same study type (e.g.,
80 pharmacokinetic, in vitro, clinical)⁹
81

82 This guidance provides additional detail and recommendations concerning:
83

- 84 • What inquiries FDA considers to be controlled correspondence for the purposes of
85 meeting the Agency’s GDUFA II commitment
86
- 87 • What information requestors should include in a controlled correspondence to facilitate
88 FDA’s consideration of and response to a controlled correspondence
89
- 90 • What information FDA will provide in its communications to requestors that have
91 submitted controlled correspondence
92
- 93 • How requestors can submit requests to clarify ambiguities in FDA’s controlled
94 correspondence response and the Agency’s process for responding to those requests
95

96

97 III. CONTROLLED CORRESPONDENCE

98

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

101

102 A. Guidance on Inquiries Within the Scope of Controlled Correspondence

103

104 1. Controlled Correspondence Issues Related to a Pending Citizen Petition

105

106 If a controlled correspondence is submitted that raises an issue that relates to one or more
107 pending citizen petitions, the 60- or 120-day time period starts on the date FDA responds to the
108 petition (if there is only one petition) or the last pending petition.¹⁰ FDA will notify the
109 requestor if the Agency determines that the controlled correspondence is related to an issue
110 raised in a pending citizen petition. When the Agency issues the citizen petition response, it will
111 commence consideration of the controlled correspondence. FDA will not notify the requestor
112 when review of the controlled correspondence has commenced; the requestor can monitor the
113 current status of the citizen petition at <https://www.regulations.gov>.

114

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

116

117 FDA occasionally receives requests for information on issues that the Agency is considering, but
118 for which no scientific or regulatory decision has been made or for which there is no clear
119 clinical consensus. For a request for which controlled correspondence is the appropriate pathway
120 but the subject is still under consideration at the time of the response goal date, FDA will notify
121 the requestor that the goal date has been missed because the request raises issues about which

⁹ Id. at 25.

¹⁰ Id. at 9.

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122 FDA has not made a decision. In such instances, the request will remain open until FDA issues a
123 response.

124

B. Guidance on Inquiries Outside the Scope of Controlled Correspondence

126

1. Requests More Appropriately Addressed Through Other Mechanisms

128

129 In certain circumstances, controlled correspondence may not be the optimal mechanism to gain
130 FDA feedback on a topic. For example, a pre-ANDA meeting¹¹ may provide a better forum in
131 which to discuss certain issues, such as methods of characterization for complex products or
132 clinically critical BE considerations. Other topics that are general in nature would be more
133 appropriately considered as part of the Regulatory Science Initiative, such as the proposed use of
134 in vitro data to support demonstration of BE for a class of RLD products for which no ANDAs
135 have been submitted. For such questions, the Agency will notify the requestor of the
136 recommended alternative pathway and close the control.¹²

137

2. Exceptions to the Definition of Controlled Correspondence

138

139
140 Historically, FDA has treated three types of inquiries that fall within the above definition of
141 *controlled correspondence* differently from other inquiries on generic drug development: (1)
142 requests for recommendations on the appropriate design of BE studies for a specific drug product
143 (BE guidance requests); (2) requests for review of BE clinical protocols (clinical protocol
144 requests); and (3) requests for meetings to discuss generic drug development before ANDA
145 submission (pre-ANDA meeting requests). FDA's process to respond to these inquiries, as
146 outlined in the GDUFA II Commitment Letter, is described further below.

147

148 First, FDA will continue to address BE guidance requests consistent with the public process
149 described in the Agency's guidance for industry on *Bioequivalence Recommendations for*
150 *Specific Products* and FDA's good guidance practices regulation.¹³ Under this approach, FDA
151 publishes BE recommendations in product-specific guidances, the availability of which is
152 announced in the *Federal Register*; they are then open to public comment for a designated
153 period. The product-specific guidance process enhances transparency, provides a mechanism for
154 public comment on recommended BE studies, provides for more efficient use of Agency
155 resources, and follows FDA's good guidance practices regulation.

156

¹¹ 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. 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. 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 review process.

¹² 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.

¹³ 21 CFR 10.115.

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157 With this public process, FDA can be proactive in developing and publishing guidance for new
158 drug products without waiting for inquiries on BE methodologies from individual requestors.
159 FDA anticipates that this process will continue to expedite the availability of BE methodologies
160 to generic drug manufacturers. This process involves time frames that differ from the goal dates
161 for controlled correspondence, however, and the Agency has determined that it would not be
162 appropriate to circumvent this public process by responding to individual requestors to meet the
163 GDUFA II goal dates for controlled correspondence because we believe public input is important
164 to the development of BE methodologies.¹⁴ The Agency will continue to consider BE guidance
165 requests in prioritizing BE guidance development.¹⁵
166

167 Second, FDA will continue to exclude requests for BE clinical protocol review from controlled
168 correspondence and the related goal dates if the RLD product is not subject to REMS ETASU.
169 These requests include requests for review of protocols for in vivo BE studies with
170 pharmacokinetic, pharmacodynamic, or clinical endpoint studies conducted to support
171 demonstration of BE for a proposed generic product. Historically, FDA has not considered such
172 requests as controlled correspondence because these requests are more time- and resource-
173 intensive than other requests and often call for consultation with multiple disciplines within the
174 Office of Generic Drugs (OGD), as well as with other offices or centers (e.g., the Center for
175 Devices and Radiological Health). Below are recommended alternatives to submitting a request
176 for BE clinical protocol review:
177

- 178 • If the request for BE clinical protocol review is intended to address a specific question
179 not covered by a product-specific BE guidance, FDA recommends that in lieu of
180 submitting a request for BE clinical protocol review, parties submit a controlled
181 correspondence requesting FDA to comment on the specific question.
182
- 183 • If the request for BE clinical protocol review involves the evaluation of a BE study
184 design that deviates from the BE studies recommended in the available product-specific
185 guidance, FDA recommends that in lieu of submitting a request for BE clinical protocol

¹⁴ 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.)

¹⁵ 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 representatives can submit controlled correspondence to GenericDrugs@fda.hhs.gov 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 draft guidance to support development of a generic drug product, the requestor can submit an inquiry as a controlled correspondence.

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186 review, parties submit a controlled correspondence requesting FDA evaluate the
187 alternative approach.

- 188
- 189 • If the request for BE clinical protocol review involves multiple questions or complex
190 issues, FDA recommends that in lieu of submitting a request for BE clinical protocol
191 review, parties submit a pre-ANDA meeting¹⁶ request or a controlled correspondence.

192

193 Third, FDA will not treat pre-ANDA meeting requests as controlled correspondence because
194 such requests serve a different purpose than controlled correspondence and should include
195 different information from the requestor. The purpose of the controlled correspondence process
196 is to provide a mechanism for a direct inquiry on FDA's position with respect to a particular
197 element of generic drug development and for the Agency's direct, brief, and timely response.
198 The purpose of a pre-ANDA meeting request, by contrast, is to seek a dialogue with the Agency
199 on a particular matter for which the controlled correspondence process is not suitable (e.g.,
200 methods of characterization for complex products or clinically critical BE considerations).
201 Similarly, materials and information submitted with a controlled correspondence should provide
202 the Agency with the relevant information on which to base its considerations, while the materials
203 submitted in support of a meeting request should help the Agency determine whether a meeting
204 is appropriate. Accordingly, we will treat pre-ANDA meeting requests separately.

205

206 We recommend that parties submit requests for recommendations on the appropriate design of
207 BE studies for a specific drug product, for review of BE clinical protocols, and for meetings to
208 discuss generic drug development before ANDA submission to GenericDrugs@fda.hhs.gov.¹⁷

209 *3. Topics Outside the Scope of Controlled Correspondence*

210

211 This section provides additional guidance on the types of inquiries or topics that do not fall
212 within the definition of standard or complex controlled correspondence described above. First,
213 the Agency considers any question related to a specific pending or approved ANDA to be
214 outside the scope of a controlled correspondence. Such inquiries should be submitted only to the
215 ANDA so they can be included as part of the full administrative record for that application.¹⁸

216

217

218 Second, inquiries that are submitted to FDA that are not directly related to generic drug
219 development will not be considered controlled correspondence for the purposes of GDUFA II.

¹⁶ 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.

¹⁷ This email address is a general OGD address to which certain submissions related to generic drugs may be submitted. This email address is monitored daily and submissions, including BE guidance requests, clinical protocol requests, pre-ANDA meeting requests, and controlled correspondence are routed to the appropriate discipline or personnel.

¹⁸ 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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220 For example, inquiries requesting information on the administrative practices of OGD, or on
221 development of generic products for which there has never been a U.S.-approved RLD identified
222 in FDA’s *Approved Drug Products with Therapeutic Evaluations* (the Orange Book), will not be
223 considered controlled correspondence.

224
225 Third, as reflected in the definition of controlled correspondence, FDA expects that a controlled
226 correspondence will contain inquiries on a specific element of generic drug development or
227 postapproval submission requirements and not general questions related to product planning.
228 Consistent with FDA’s past and current practices, general or insufficiently detailed questions
229 related to product development are not the appropriate subject of controlled correspondence. For
230 example, an inquiry seeking information on general approval standards for a particular product is
231 not the appropriate subject of a controlled correspondence for the purposes of GDUFA II.
232 Likewise, an inquiry about the acceptability of an excipient without a proposed level for a
233 specific RLD (which includes a specific product strength) or a question about the general
234 acceptability of a particular device provides insufficient detail for the Agency to respond. FDA
235 provides information to stakeholders on its approval standards and general submission
236 recommendations through FDA regulations and guidances, and the Agency encourages generic
237 drug manufacturers and related industry to review this information before submitting controlled
238 correspondence to OGD. The controlled correspondence process is intended to facilitate, not
239 supplant, the generic drug development endeavor.

4. Entities Outside the Scope of Controlled Correspondence

240
241
242
243 The controlled correspondence process, historically (and under the definition above), is available
244 to generic drug manufacturers and related industry or their authorized representatives (see below)
245 that have a question related to a potential ANDA submission to OGD, because this mechanism
246 exists to facilitate generic drug development. Other parties (e.g., private citizens, financial firms,
247 or public advocacy groups that are not directly involved in developing generic drug products)
248 should submit their inquiries related to generic drugs to the Division of Drug Information.¹⁹

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

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250
251
252
253 As stated in the GDUFA II Commitment Letter, FDA will “[c]ontinue to review and act on . . .
254 controlled correspondence submitted prior to October 1, 2017 that have been assigned GDUFA I
255 goal dates pursuant to the GDUFA I review metrics applicable to those submissions.”²⁰ For any
256 controlled correspondence submitted during GDUFA I for which FDA issued a response after
257 October 1, 2017, and for which a submitter requests clarification of ambiguities in the controlled
258 correspondence response (see section V.B. below), FDA will grant such a request for
259 clarification, when possible, within the performance goal identified in the GDUFA II
260 Commitment Letter.²¹

261

¹⁹ See contact information for the Division of Drug Information on the second title page of this guidance.

²⁰ 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.

²¹ See GDUFA II Commitment Letter at 9.

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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 electronically, via email to GenericDrugs@fda.hhs.gov. This will facilitate prompt consideration of and response to the controlled correspondence by the appropriate discipline. The email should be sent from a corporate email address. We do not intend to consider emails generated from general, personal accounts as controlled correspondence. If 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 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 email 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 a controlled correspondence be submitted on corporate letterhead, as an attachment to the email, and with the following information included at the beginning of the controlled correspondence:

- Name, title, address, phone number, and entity (e.g., corporate affiliation) of the person submitting the controlled correspondence. The controlled correspondence must be submitted by an authorized representative of the generic drug manufacturer or related industry, its authorized agent, or the agent’s authorized representative, located in the United States.²²
- Please identify the company for which you are the authorized agent and include a copy of a letter of authorization with each controlled correspondence.²³ The letter of authorization should be dated within one year of the date the controlled correspondence is submitted. FDA intends to provide a response to the U.S.

²² See the definition of controlled correspondence in the September 2015 guidance for industry, *Controlled Correspondence Related to Generic Drug Development*, which has been incorporated into this guidance (“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”).

²³ 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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301 authorized agent or the agent's authorized representative of a foreign company,
302 similar to FDA practice when an ANDA is submitted.
303

- 304 • FDA-assigned control number and submission date of any previous, related controlled
305 correspondence that was accepted for substantial review and response, if any, as well as a
306 copy of that previous controlled correspondence and FDA's response, if any.
307
- 308 • Relevant RLD(s), as applicable, including application number, proprietary (brand) name,
309 manufacturer, active ingredient, dosage form, and strength(s).
310
- 311 • Statement that the controlled correspondence is related to a potential ANDA submission
312 to OGD. Include the ANDA number if the controlled correspondence is related to a
313 submitted ANDA,²⁴ including an ANDA that FDA has refused to receive, or if the
314 controlled correspondence is related to a potential and not yet submitted ANDA that has
315 already been assigned an ANDA number.
316
- 317 • Concise statement of the inquiry for which the controlled correspondence is being
318 submitted.
319
- 320 • Recommendation of the appropriate FDA review discipline to review the controlled
321 correspondence. General information regarding review disciplines is provided in section
322 IV.D. below.
323
- 324 • Relevant prior research and supporting materials.
325

326 FDA recommends that requestors include in their controlled correspondence the pertinent
327 prior research and supporting information on the specific element of generic drug
328 development about which they seek information. If FDA determines that the inquiry
329 does not contain the information specified in the bulleted list in this section, the inquiry
330 will not be considered to be submitted for purposes of GDUFA II. If FDA determines,
331 during the substantive review of the inquiry, that the inquiry lacks sufficient information,
332 it can either close the control at that time or contact the requestor for additional
333 information. If the Agency decides to close the control, it will notify the requestor of that
334 decision and the basis for that decision. If FDA contacts the requestor for additional
335 information, the GDUFA II goal date for that controlled correspondence will be extended
336 by the amount of time that the Agency's request for additional information is outstanding
337 with the requestor.
338

C. Additional Recommendations on the Content of Specific Types of Controlled 340 Correspondence Inquiries

341

²⁴ 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 18.

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

344

1. Requests Related to Inactive Ingredients

346

347 The Agency often receives requests for information pertaining to whether particular inactive
348 ingredients present at higher levels than the maximums listed in the Agency's Inactive Ingredient
349 Database are permissible in a generic drug product.²⁵ FDA recommends that a requestor submit
350 for evaluation no more than three inactive ingredients and no more than three proposed
351 formulations total for a drug product, in any given controlled correspondence. For example, a
352 request that proposes three different levels for a single inactive ingredient would be considered to
353 include three proposed formulations, and a requestor should wait for FDA's response to the
354 controlled correspondence before submitting a different formulation for consideration. The
355 Agency believes this is the reasonable limit based on what can be evaluated for a particular drug
356 product within the GDUFA II goal date period. This encourages applicants to provide targeted
357 submissions to the Agency and allows applicants to refine their subsequent formulation
358 proposals based on FDA's previous responses. In addition, such requests should identify the
359 RLD (including the specific drug product strength(s)) to allow FDA to evaluate the potential
360 acceptability of an excipient in the context of a specific proposed drug product. Absent that
361 information, there is no means for FDA to evaluate the safe use of that inactive ingredient, which
362 depends on many factors, including the conditions of use (i.e., indicated population including
363 pediatrics, route of administration, duration of use) for the RLD. Although FDA may provide
364 advice regarding an inactive ingredient through a controlled correspondence, FDA evaluates the
365 ultimate acceptability of an inactive ingredient in the context of a specific proposed drug product
366 formulation during ANDA review, when the Agency has the full complement of data and
367 information in support of ANDA approval to consider.

368

2. Requests for Q1/Q2 Formulation Assessment

370

371 For certain types of products, FDA's regulations generally require that proposed products be
372 qualitatively (Q1) and quantitatively (Q2) the same as the RLD with respect to inactive
373 ingredients.²⁶ In addition, FDA's guidances sometimes recommend certain BE studies for drug
374 products that are Q1/Q2 with respect to the RLD. When seeking review of proposed Q1/Q2
375 formulations, we recommend the controlled correspondence include the following information
376 about the RLD (which can be found in the Orange Book):

377

- 378 • Relevant RLD application holder
- 379 • Application number
- 380 • Proprietary name
- 381 • Active ingredient

²⁵ 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>

²⁶ See, e.g., 21 CFR 314.94(a)(9)(iii).

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- 382 • Dosage form
- 383 • Route of administration
- 384 • RLD approval date
- 385 • Market status (i.e., whether the product is prescription, over-the-counter, or in the
- 386 “Discontinued” section of the Orange Book, which lists drug products that have been
- 387 withdrawn from the market)
- 388

389 FDA recommends that no more than three proposed Q1/Q2 formulations of a single drug product
390 be submitted in one controlled correspondence. Limiting a single control to no more than three
391 formulation requests provides for FDA’s targeted and timely review of such requests. In
392 addition, the Agency recommends against submitting a request for a Q1/Q2 formulation
393 assessment and a separate request for evaluation of a proposed inactive ingredient amount or
394 concentration at the same time. The formulation descriptions should include adequate details,
395 including salt and hydration forms, purity, and function of the active ingredients and
396 excipients.²⁷

397
398 If a requestor is seeking formulation assessment for multiple drug products, FDA recommends
399 that each drug product request be submitted in a separate controlled correspondence. Thus, a
400 requestor should not seek Q1/Q2 formulation assessment for generic drugs with different RLDs
401 in a single controlled correspondence. This also includes separate formulation assessment
402 requests for drug products with multiple strengths, because each strength is a separate drug
403 product. It should be noted that Agency policy or regulation may limit the amount or type of
404 information that FDA may disclose in response to a request for Q1/Q2 formulation assessment.²⁸

405
406 Consistent with the Agency’s past and current practices, FDA does not intend to review
407 proposed formulations that are neither required by regulation nor recommended in guidance to
408 be Q1/Q2 to the RLD. Non-Q1/Q2 formulations are permissible for certain products so long as
409 the differences do not affect the safety or effectiveness of the product. The acceptability of such
410 differences would be considered in the context of an ANDA review. FDA also does not intend
411 to provide clarification on why a formulation is not Q1/Q2 (see section V.B. below).²⁹

412 413 *3. Requests Related to Product Quality*

414
415 The Agency often receives requests for information pertaining to chemistry, manufacturing, and
416 controls for generic drugs and inquiries related to Type II drug master files for drug substances
417 submitted in support of generic drug applications. FDA recommends that a requestor include
418 prior research and supporting product quality information in the controlled correspondence to
419 adequately respond to the inquiry. The level of detail of the supporting product quality
420 information should be commensurate with the question(s) being asked. Typically, a submission
421 related to product quality would include, as applicable, a brief description of the proposed

²⁷ 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.

²⁸ See e.g., 21 CFR 20.61(a) and (b).

²⁹ Id.

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422 formulation, manufacturing process, container-closure system, and developmental studies. For
423 example: (1) an inquiry on stability bracketing/matrixing design should include whether a
424 common blend is used to make the drug product, proposed product strengths, storage conditions,
425 and a description of the container-closure system, including any other necessary information to
426 justify the reduced stability design; and (2) a question on size, shape, or other physical attributes
427 of a drug product should be supported by comparative data of the proposed generic drug product
428 and RLD with regard to product dimensions, volume, images, and other relevant properties. A
429 detailed description, with relevant prior research and supportive information, in a controlled
430 correspondence will increase the likelihood that FDA will have the necessary information to
431 provide a specific response to the inquiry.

432 *4. Requests Requiring Review by More Than One Discipline*

433
434 If a requestor seeks information related to separate elements of generic drug product
435 development requiring review by more than one discipline (e.g., information on proposed
436 formulation and proposed product labeling), FDA recommends that the requestor submit separate
437 requests regarding the product.³⁰ This will facilitate timely review and response.
438

439 *5. Requests Concerning Postapproval Submission Requirements*

440
441 As indicated in the definition of standard controlled correspondence, FDA will respond to
442 controlled correspondence seeking information on postapproval submission requirements.³¹
443 FDA will only respond to correspondence requesting information on postapproval submission
444 requirements that are not covered by existing guidance on postapproval changes.³² Further, the
445 request must not be related to a specific ANDA.³³ Postapproval controlled correspondence
446 includes, but is not limited to, specific questions related to a product site transfer that would
447 affect more than one approved ANDA and specific questions related to modernizing a
448 manufacturing facility that is approved for more than one ANDA.
449

450 *6. Complex Controlled Correspondence*

451
452 Pursuant to the GDUFA II Commitment Letter, the definition of complex controlled
453 correspondence includes controlled correspondence involving evaluation of clinical content, BE
454 protocols for RLDs with REMS ETASU, or requested evaluations of alternative BE approaches
455 within the same study type (e.g., pharmacokinetic, in vitro, clinical).³⁴
456

³⁰ 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 substantial review and response.

³¹ GDUFA II Commitment Letter at 27-28.

³² 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>.

³³ GDUFA II Commitment Letter at 27-28.

³⁴ Id. at 25.

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

466
467 FDA will continue to address requests regarding BE protocols for RLDs with REMS ETASU
468 consistent with the process described in the Agency’s guidance for industry *How to Obtain a*
469 *Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections*
470 *Comparable to Applicable REMS for RLD.*

471
472 FDA will consider requests to evaluate alternative BE approaches within the same study type
473 (e.g., pharmacokinetic, in vitro, clinical) to be complex controlled correspondence for drug
474 products for which a product-specific BE guidance is available to industry.

D. Controlled Correspondence Review Disciplines

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477
478 This section provides additional information on the different disciplines that might review and
479 respond to a controlled correspondence. In addition, this section provides examples of the types
480 of inquiries each discipline might review. The Agency anticipates that this information will
481 assist requestors in recommending the appropriate discipline to review a particular controlled
482 correspondence, as suggested above in section IV.B. These descriptions are not intended to be
483 exhaustive, and FDA has the discretion to determine which discipline should review and respond
484 to a controlled correspondence.

1. OGD’s Office of Bioequivalence

485
486
487
488 FDA anticipates that the Office of Bioequivalence will review correspondence containing
489 inquiries related to the planning of BE studies, including the review of protocols for drug
490 products subject to REMS ETASU. The Office of Bioequivalence will also review questions
491 related to the maximum daily exposure of an inactive ingredient.

2. OGD’s Office of Research and Standards

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494
495 FDA anticipates that the Office of Research and Standards will review correspondence
496 containing questions on complex products³⁵ or drug-device combination products.

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

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

³⁵ See GDUFA II Commitment Letter at 25.

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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 questions.

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

FDA anticipates that the Office of Policy for Pharmaceutical Quality will coordinate Office of Pharmaceutical Quality (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.

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 to GenericDrugs@fda.hhs.gov, FDA will provide the following information to a requestor regarding receipt and consideration of the inquiry.

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: (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;³⁶ 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, and the communication will contain a

³⁶ 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.

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544 receipt date that the requestor can use to calculate the goal date.³⁷ If a requestor resubmits a
545 request for information that addresses any problem that FDA identified with a previous request,
546 the Agency will consider this a new controlled correspondence and process it as such.

547
548 After reviewing the request for information in the controlled correspondence, FDA will respond
549 in written form via email to the email address from which the original controlled correspondence
550 was sent. FDA will only send a response to the person who originally submitted the controlled
551 correspondence. The length and content of FDA’s response will depend on the nature of the
552 inquiry submitted. We intend that the comments we provide in response to a controlled
553 correspondence will be comprehensive as of the date of the response. We note that comments in
554 the response represent our thinking on a topic at that time and that our thinking may evolve in the
555 future.

556
557 FDA will not respond to status requests regarding pending controlled correspondence before the
558 goal date.³⁸ If the Agency does not respond to the controlled correspondence by the goal date,
559 FDA will send an acknowledgement to the requestor with notification that the request is still
560 under consideration.³⁹

B. Clarification of the Controlled Correspondence Response

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562
563
564 In general, FDA considers follow-up questions to FDA’s controlled correspondence response
565 and requests for additional information as new controlled correspondence. This ensures that the
566 follow-up question is tracked and that all requestors are treated equitably. In these instances, we
567 recommend that a requestor submit a new controlled correspondence and include the FDA-
568 assigned control number of the previous inquiry to facilitate FDA’s review and response.

569
570 FDA will respond to requests to clarify ambiguities in the Agency’s controlled correspondence
571 response, and such requests may be treated differently than follow-up questions. As defined in
572 the GDUFA II Commitment Letter, ambiguity in the controlled correspondence response “means
573 the controlled correspondence response or a critical portion of it, in FDA’s judgment, merits
574 further clarification.”⁴⁰ All requests for clarification of a controlled correspondence should be
575 included in a single submission to FDA. The request for clarification should be submitted within
576 7 calendar days of issuance of FDA’s controlled correspondence response.⁴¹ Requests for

³⁷ 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.

³⁸ For pre-FY 2015 controlled correspondence, OGD will strive to respond to these controls as expeditiously as practicable.

³⁹ In circumstances in which there is a pending citizen 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 citizen petition at <https://www.regulations.gov> (see section III.A.1. of this guidance).

⁴⁰ GDUFA II Commitment Letter at 24.

⁴¹ 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.

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577 clarification received after 7 calendar days from issuance of the controlled correspondence
578 response will be considered a new controlled correspondence.

579
580 Requestors seeking clarification of ambiguities in FDA’s controlled correspondence response
581 should submit the request electronically, via email to GenericDrugs@fda.hhs.gov. The subject
582 line of the email should state that it is a “Request to Clarify Ambiguities in a Controlled
583 Correspondence Response.” The request to clarify ambiguities in the controlled correspondence
584 response should include the following information:

585
586 • Name, title, address, phone number, and entity (e.g., corporate affiliation) of the person
587 submitting the request for clarification of the controlled correspondence response. The
588 request for clarification of FDA’s controlled correspondence response must be submitted
589 by an authorized representative of the generic drug manufacturer or related industry, its
590 authorized agent, or the agent’s authorized representative, located in the United States.⁴²
591 Where possible, the request to clarify ambiguities in FDA’s controlled correspondence
592 response should be submitted by the person who originally submitted the controlled
593 correspondence on which clarification is sought. If this is not possible, FDA will accept
594 the request from an alternate, authorized representative of the generic drug manufacturer
595 or related industry, its authorized agent, or the agent’s authorized representative, located
596 in the United States.

597
598 • Please identify the company for which you are the authorized agent and include a
599 copy of a letter of authorization. The letter of authorization should be dated
600 within one year of the date the request for clarification of FDA’s controlled
601 correspondence response is submitted. FDA intends to provide a response to the
602 U.S. authorized agent or the agent’s authorized representative of a foreign
603 company, similar to FDA practice when an ANDA is submitted.

604
605 • FDA-assigned control number, submission date of the controlled correspondence on
606 which the requestor is seeking clarification, a copy of that previous controlled
607 correspondence, and FDA’s response to the controlled correspondence.

608
609 • Clarifying questions and the corresponding section(s) of FDA’s controlled
610 correspondence response on which the requestor is seeking clarification.

611
612 The scope of the clarifying questions should be limited to the content of FDA’s controlled
613 correspondence response. Any requests to review new or additional information will be
614 considered a new controlled correspondence and should be submitted as such
615 to GenericDrugs@fda.hhs.gov.

616
617 As agreed to in the GDUFA II Commitment Letter, FDA will review and respond to 90 percent
618 of requests to clarify ambiguities in the controlled correspondence response within 14 calendar
619 days of the Agency’s receipt of the request.⁴³ If FDA determines that the request does not

⁴² Supra note 22.

⁴³ 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

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

622
623 After reviewing the request for clarification, FDA, at its discretion, will either call the requestor
624 or respond in written form via email to the email address from which the request was sent to
625 clarify ambiguities in FDA's controlled correspondence response. FDA's response will either
626 clarify the ambiguity in the controlled correspondence response or state that, in FDA's judgment,
627 the controlled correspondence response does not merit further clarification.

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.